L5: Communication for organization: how cellular conversations sculpt organ-scale structures.

By the end of this lecture, you should be able to:

- Define the term 'weak emergence' in a biological context.
- Describe the main events in development of the mammalian kidney.
- Use experimental evidence to demonstrate that renal development is regulative, and not just the realization of an inflexible 'genetic blueprint'.
- Describe how cell-cell signalling achieves population balance, quorum sensing, patterning of an epithelial tree and correct vascular development
- Demonstrate that these signalling systems allow automatic correction of developmental errors.
- Identify examples of the organizational principles above in organization at smaller scales (within cells), and at much larger scales (within super-organisms and societies).

The problem:

How do cells, about 10um across and that can sense conditions only within themselves and at their surfaces, cooperate to make an organ 10cm across (10,000 x their length)?

Possible solution 1: precise working out of a 'genetic blueprint' / 'program' / 'recipe'

Possible solution 2: adaptive self-organization

(Some philosophers talk about another form, 'strong' emergence – this is essentially irrelevant to science)

('weak') EMERGENCE – the presence of properties at system-level that are not present at component level.

Homely examples:

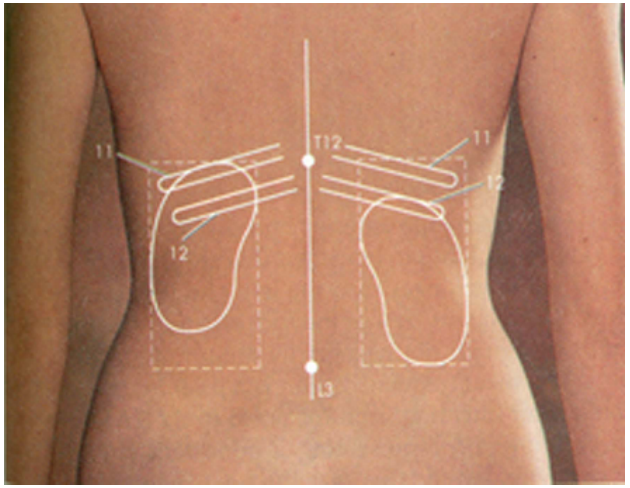
A radio works because its components are arranged in a particular way – not because any one of them has 'radio reception' as a property.

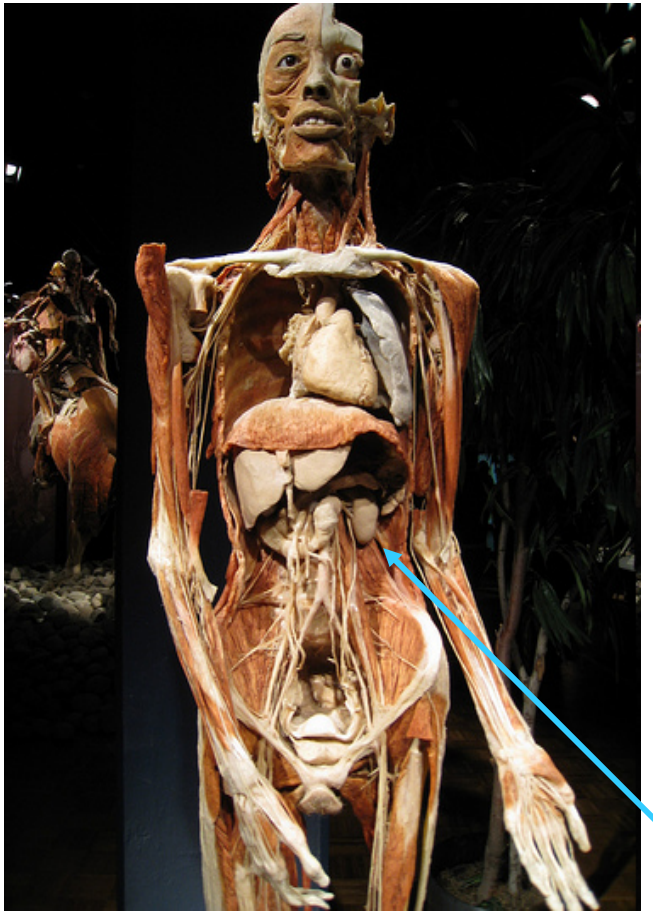
Pressure/ temperature of a gas are not properties of individual molecules

There is nothing 'special' about development of the kidney – we are using it as an example organ and the same basic messages would have appeared had we used any other organ.

"To see a World in a Grain of Sand
And a Heaven in a Flower,
Hold Infinity in the palm of your hand
And Eternity in an hour."

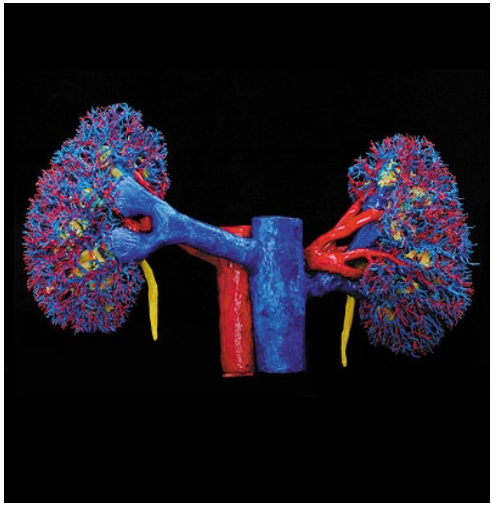
The star of this lecture: the kidney



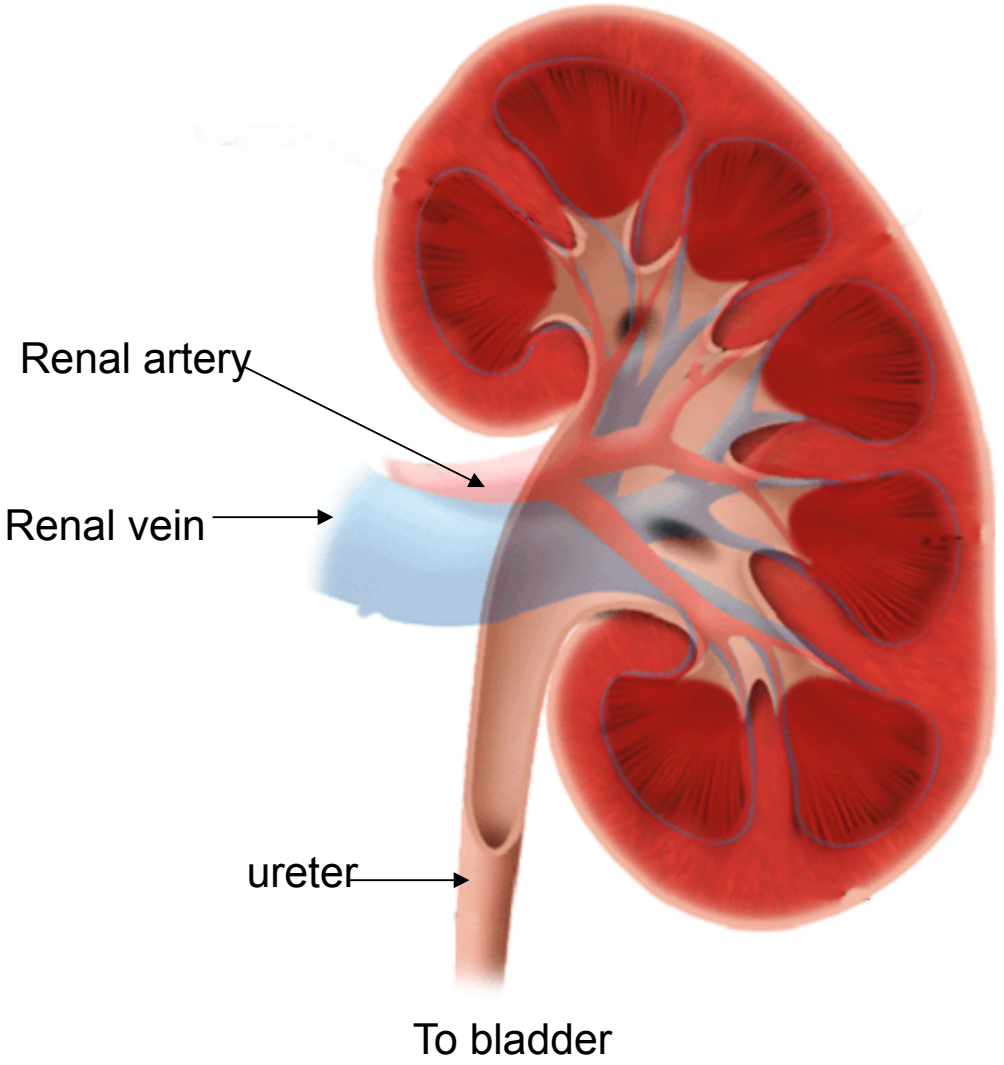


Left kidney

Source: Body Worlds

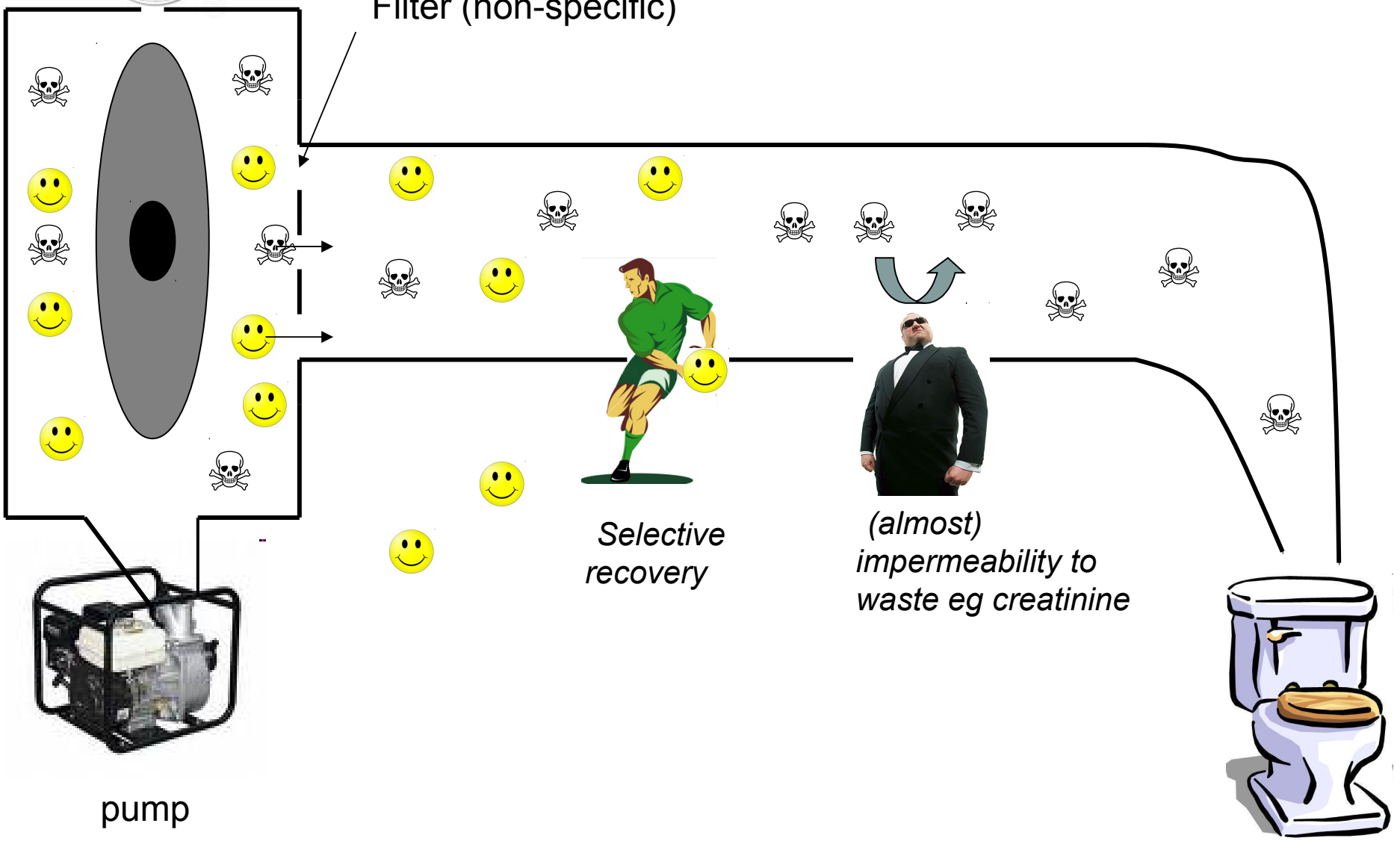


20% of cardiac output


Renal artery
Renal vein
ureter
To bladder

Functional view:

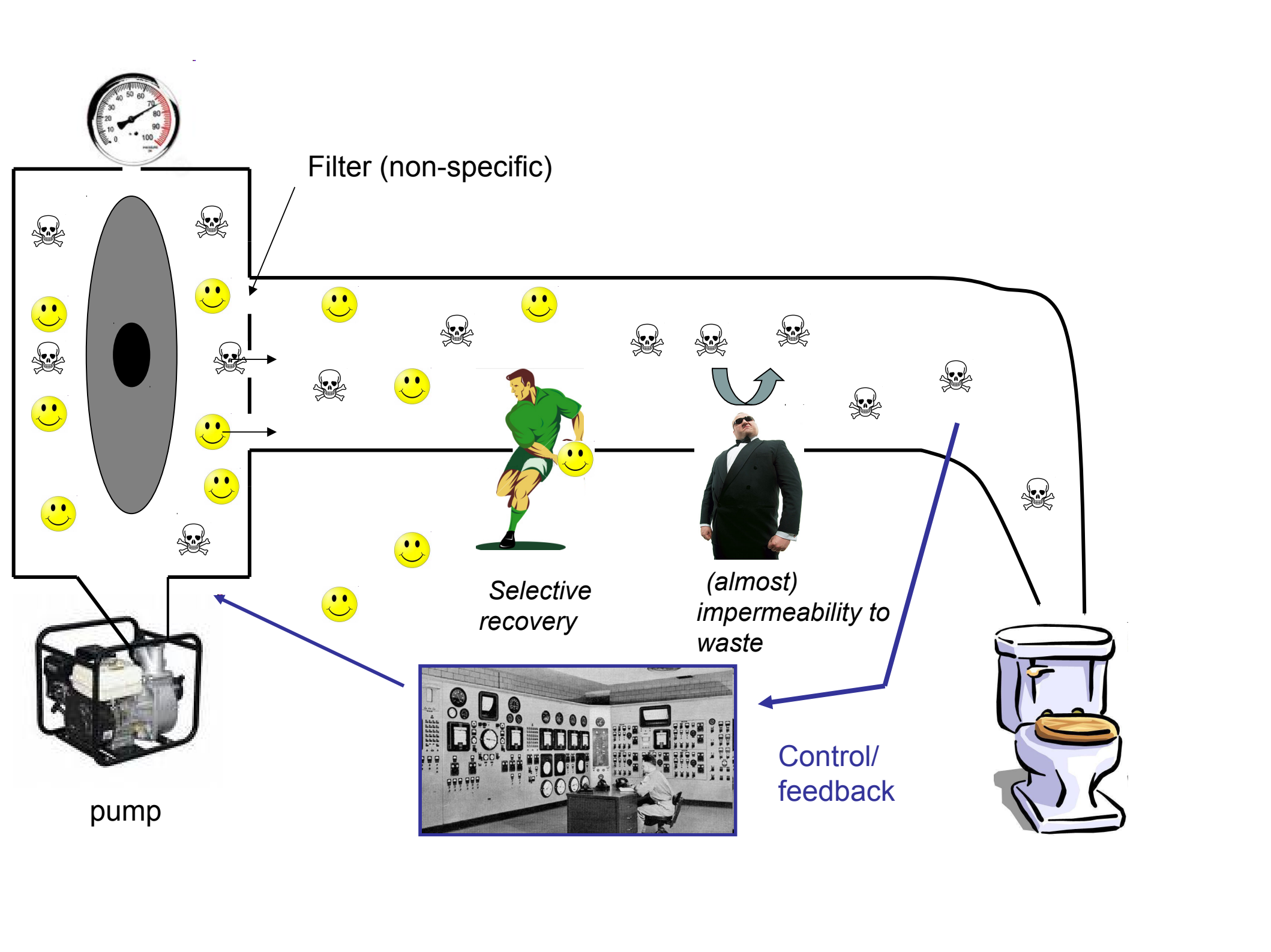
Filter (non-specific)

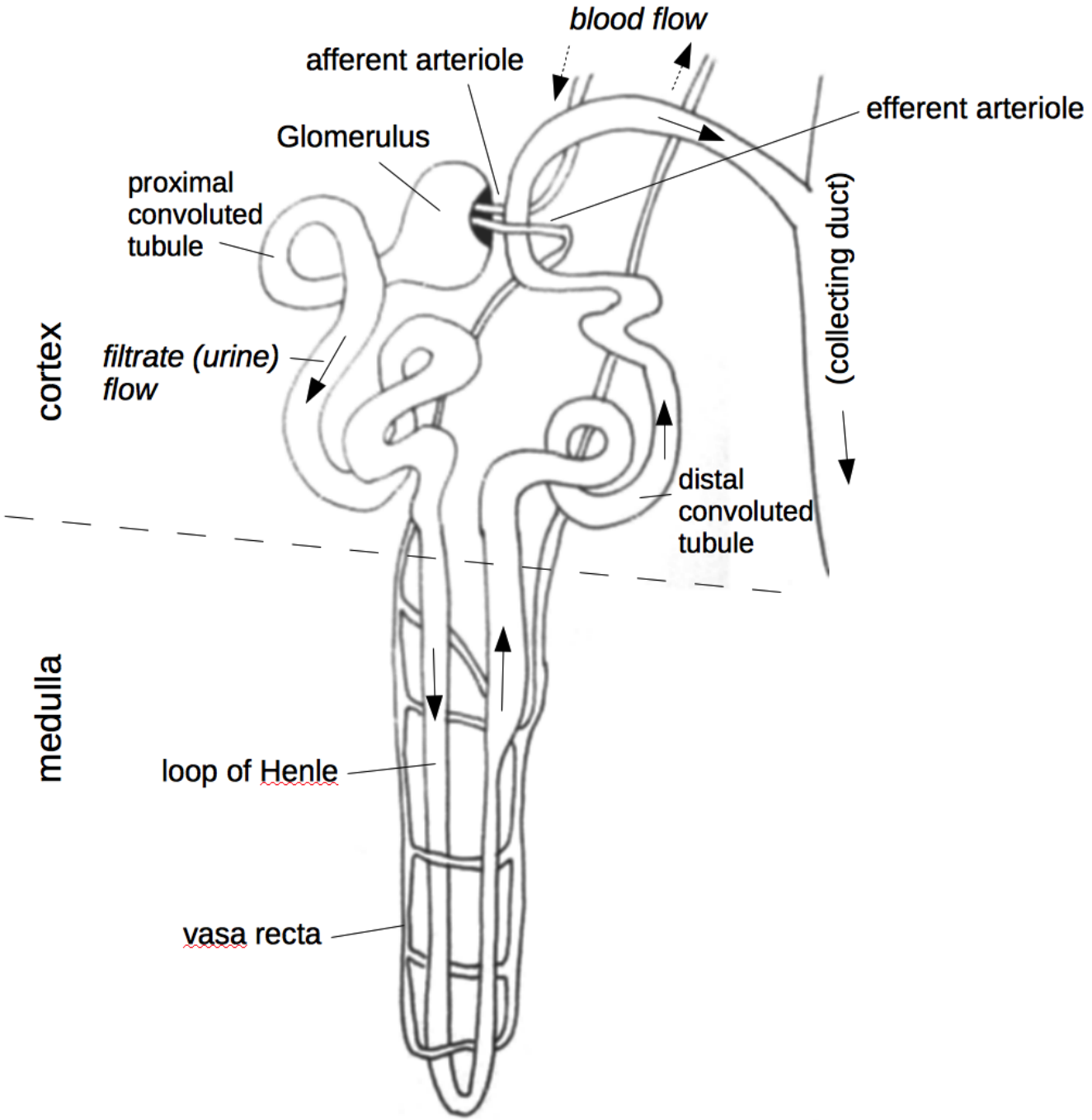


Selective recovery

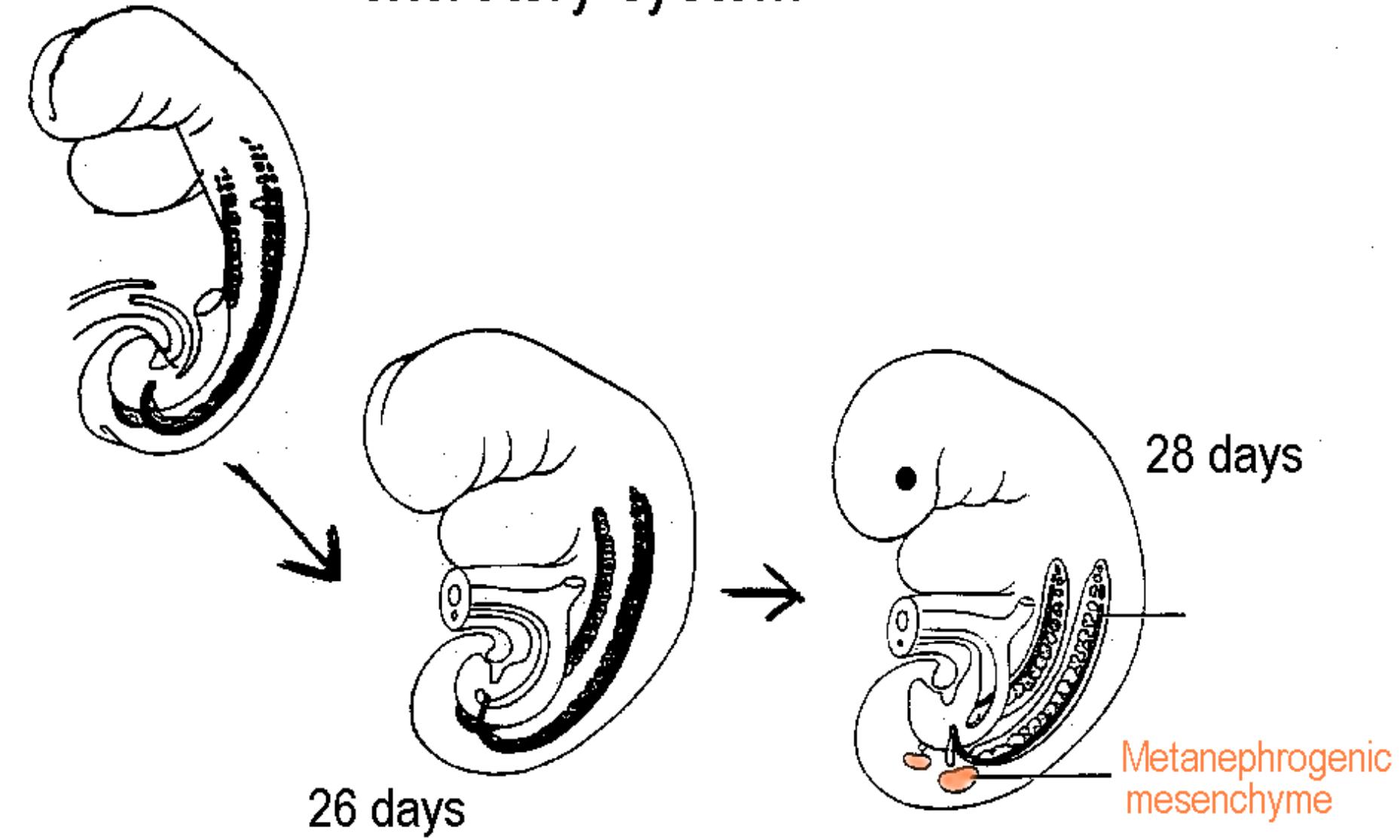
(almost) impermeability to waste eg creatinine

pump

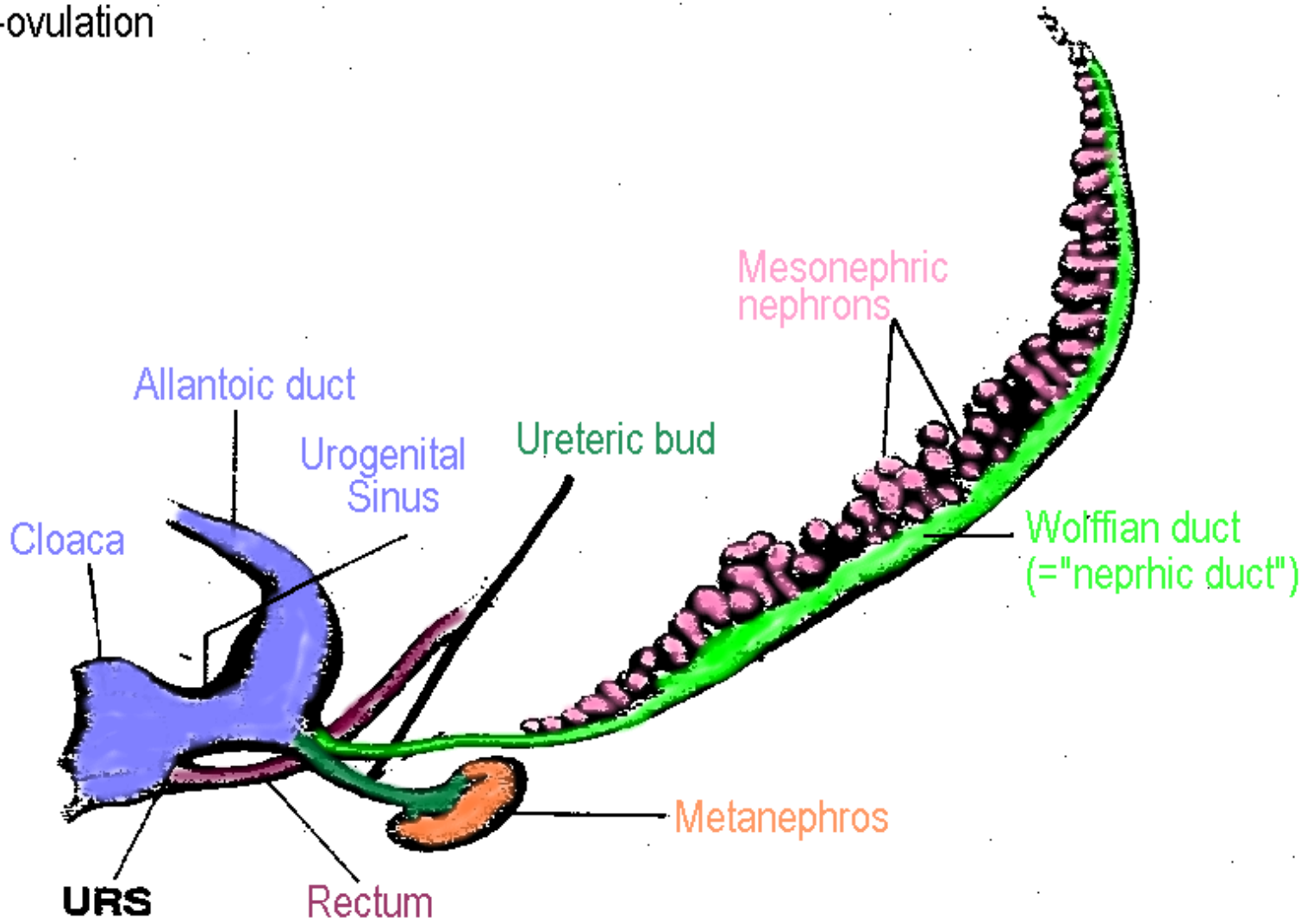

Filter (non-specific)
Selective recovery
(almost) impermeability to waste
pump
Control/ feedback


blood flow
afferent arteriole
efferent arteriole
Glomerulus
proximal convoluted tubule
(collecting duct)
cortex
filtrate (urine) flow
distal convoluted tubule
medulla
loop of Henle
vasa recta

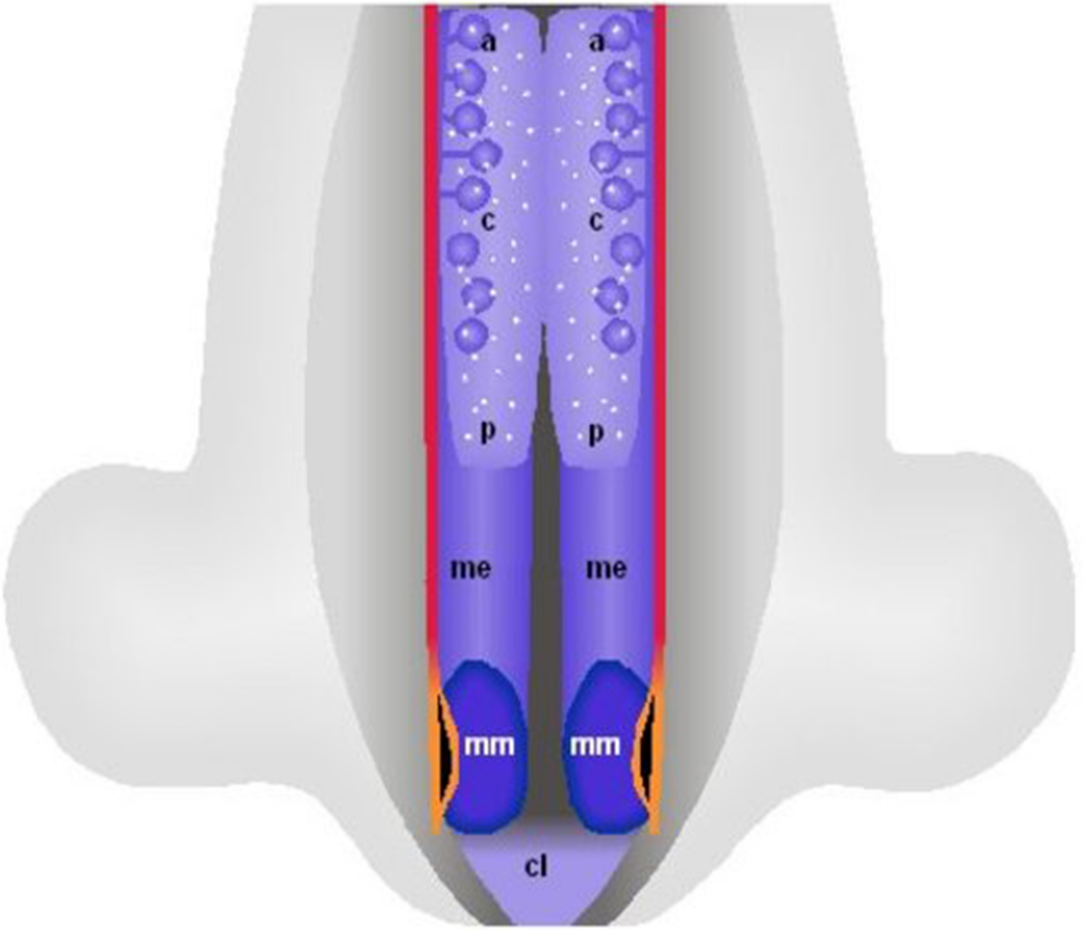
Development of the human excretory system



Scheme of the urinary tract of an 8mm human embryo
38 days post-ovulation



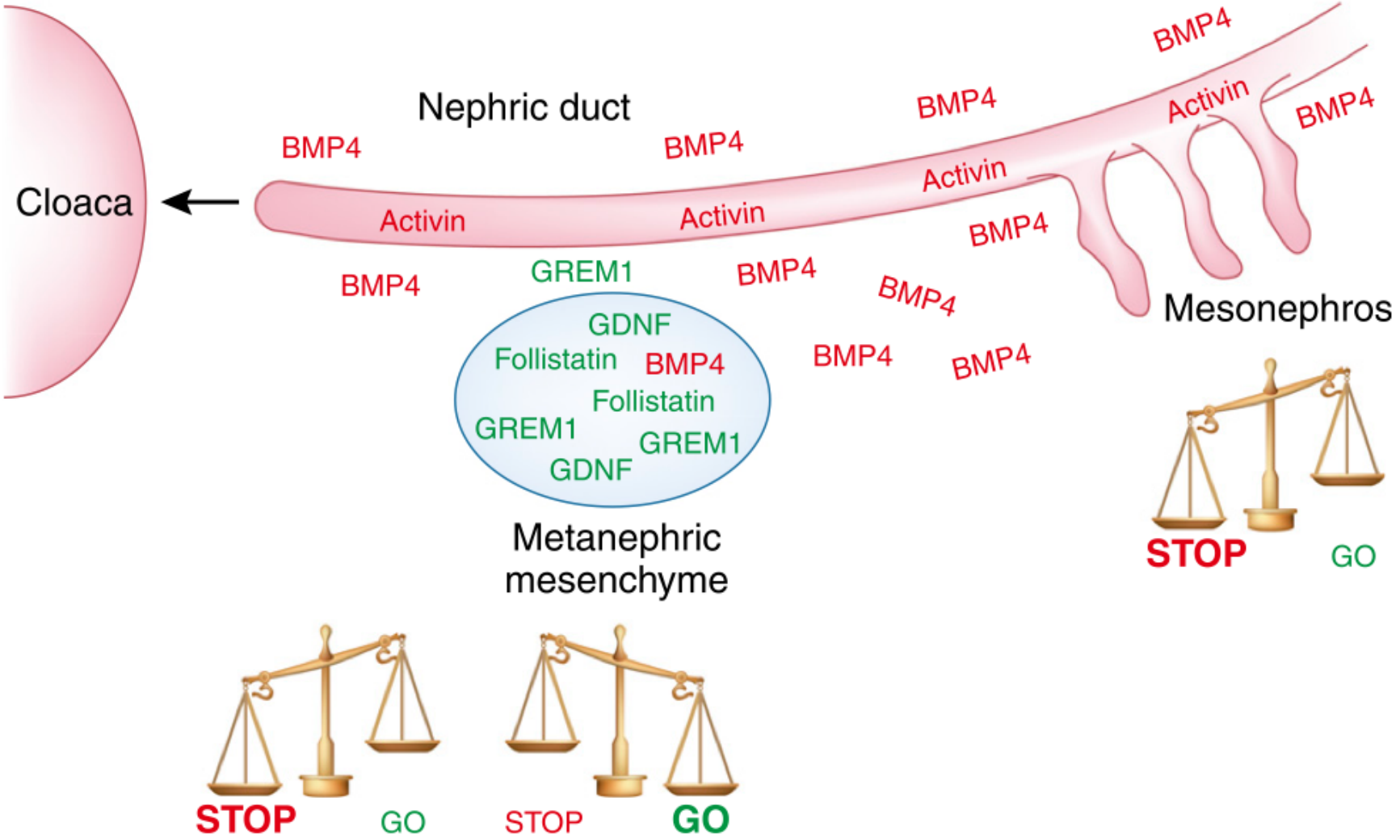
TS17 Urogenital System



From www.GUDMAP.org - CC

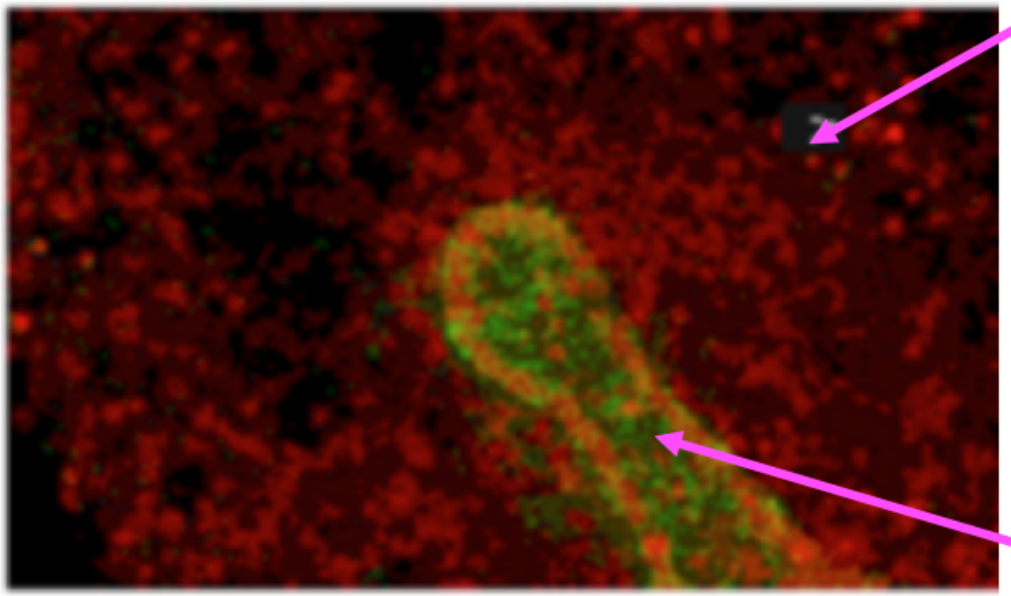
Problem 1: how to make just one ureter come out of each Wolffian duct:

Solution: a load of biochemical 'No Entry' signs where ureters are not wanted

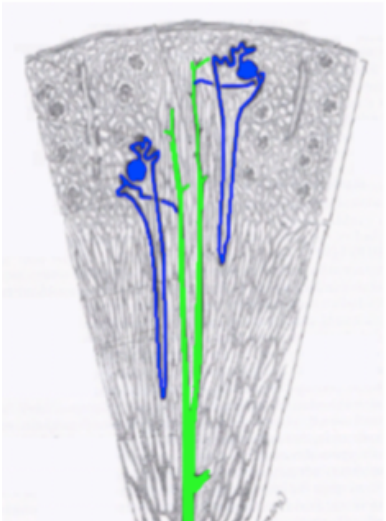


From Woolf & Davies (2012) – J Am Soc Nephrol 24:19-25

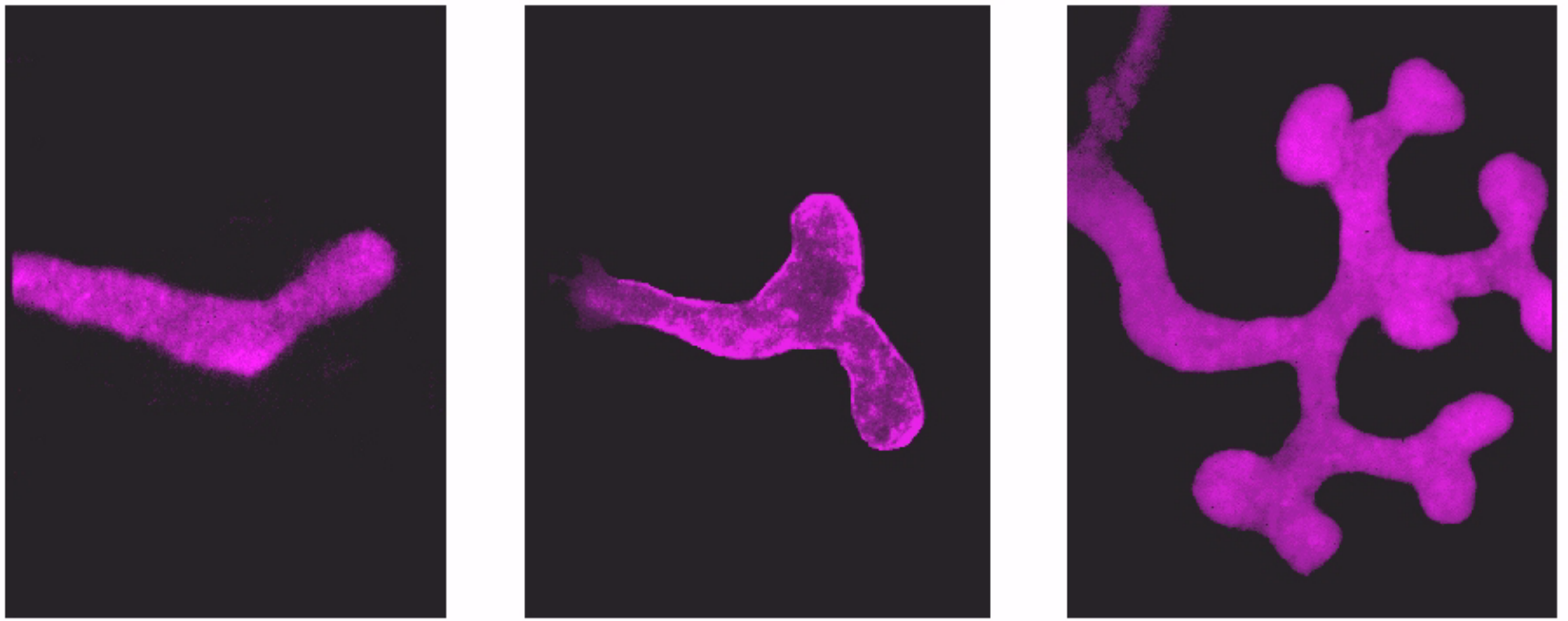
This is what the kidney area looks like just after the bud has entered the mesenchyme



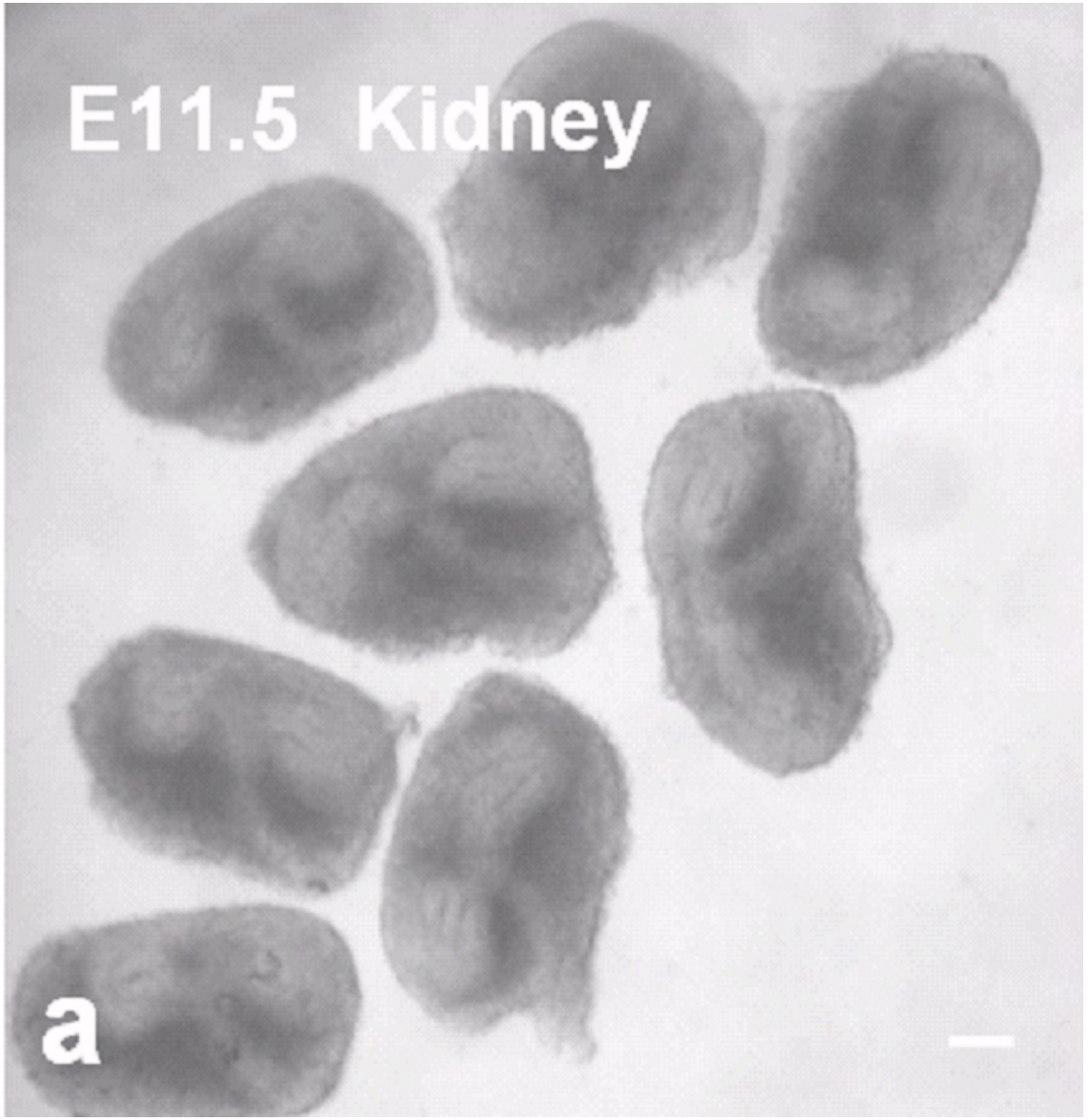
In this picture, red marks the nuclei of all cells while green stains only cells of the ureteric bud.

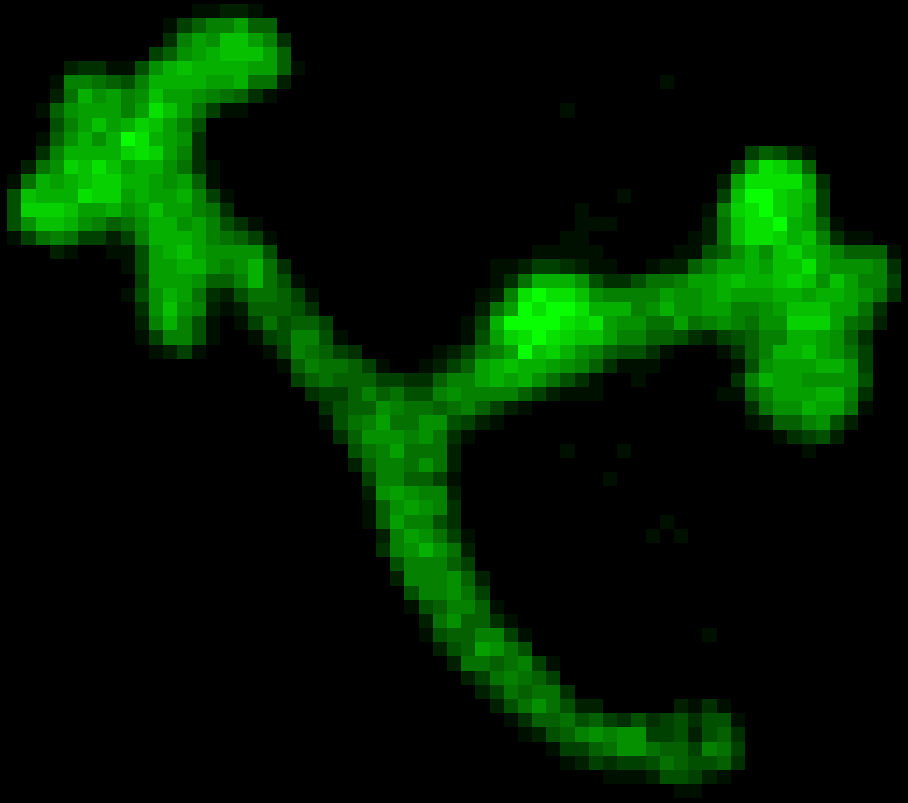


Branching of the ureteric bud



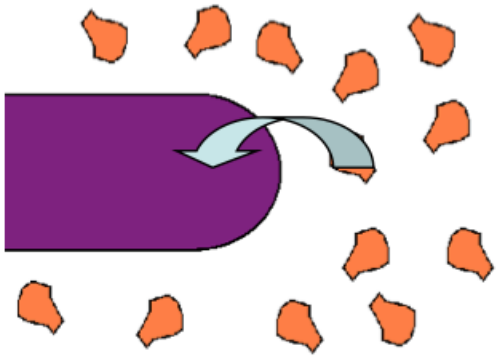
0 days 1 day 2 days


E11.5 Kidney
a



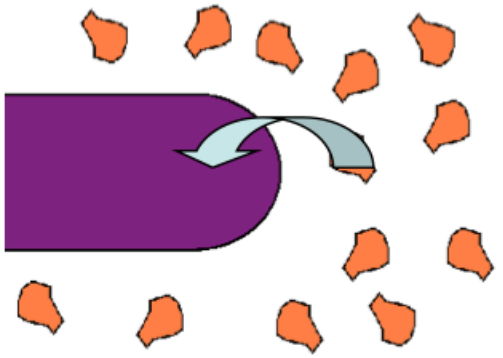
Problem 2 – how is the branching controlled?

1) GUESS that surrounding cells make signals that control the branching

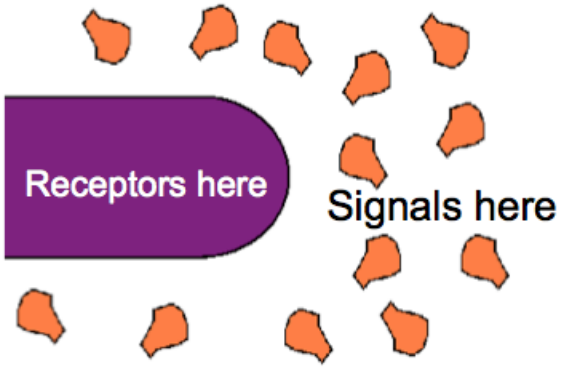


conjecture

1) GUESS that surrounding cells make signals that control the branching

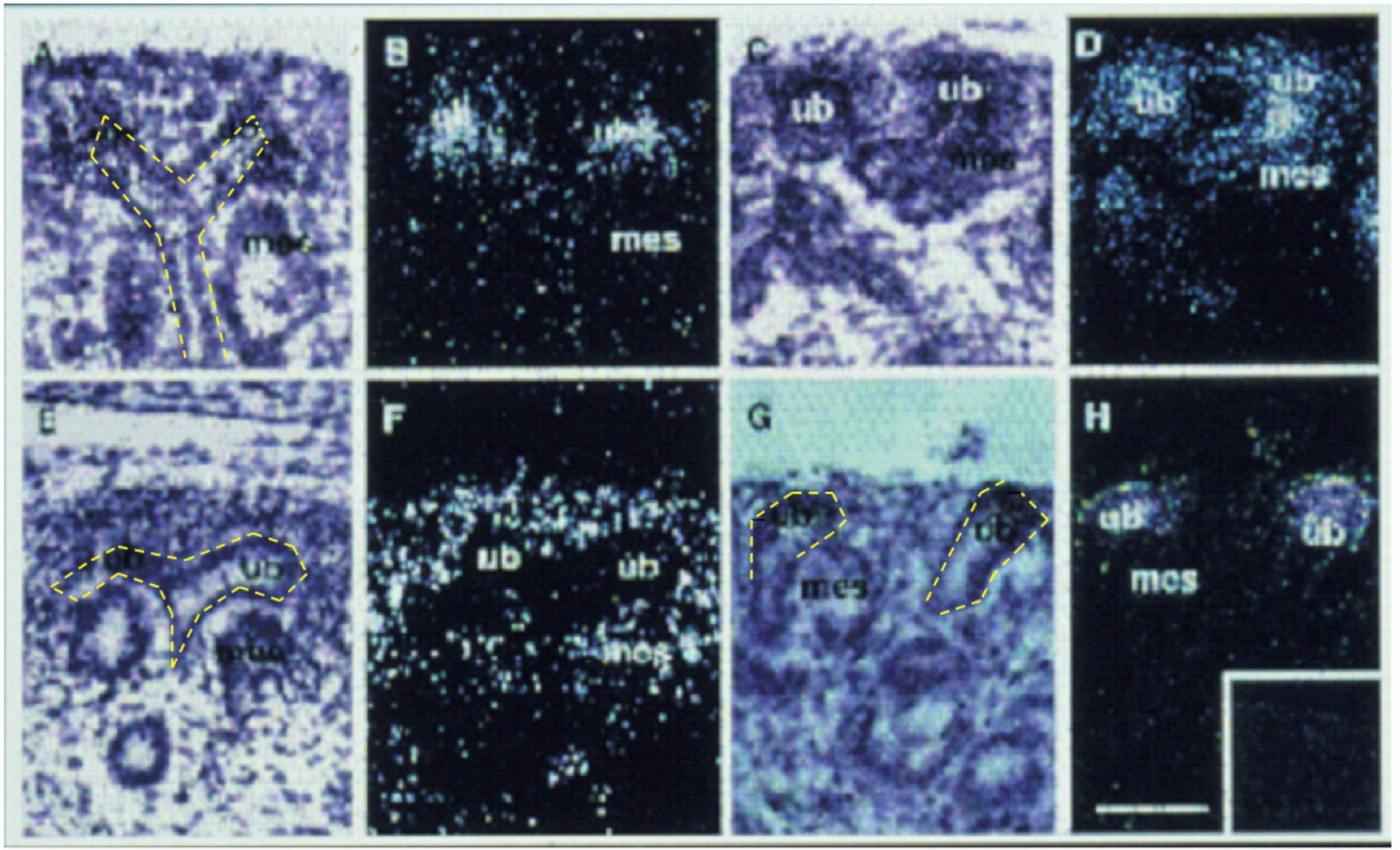


2) LOOK for signal proteins and matching receptors that are in the right place for this



Receptor (Ret)

Co-receptor (GFR1a)



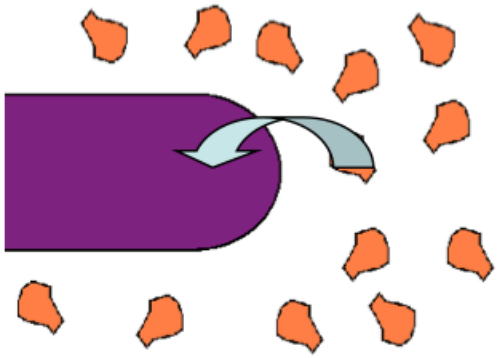
Signal (GDNF)

Actual binding of radioactive GDNF

conjecture

Refutation (or provisional acceptance)

1) GUESS that surrounding cells make signals that control the branching



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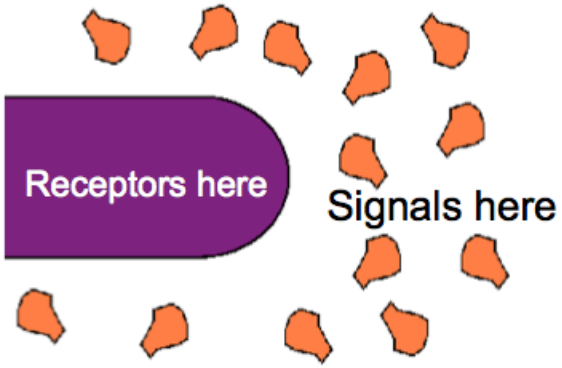


3) TEST to see if they control the bud

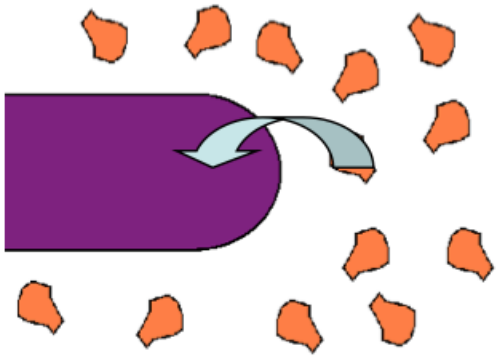
conjecture

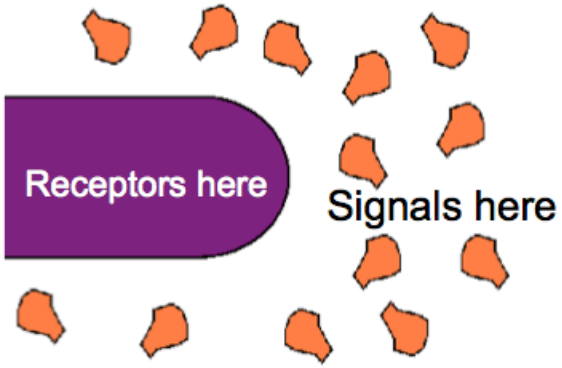
Refutation (or provisional acceptance)

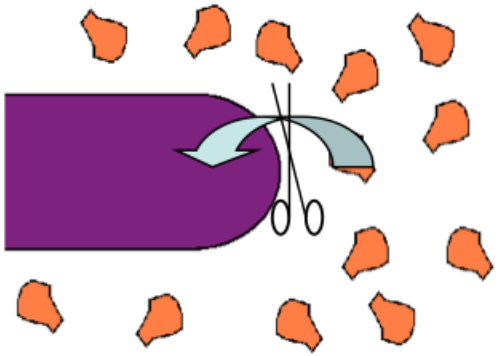
1) GUESS that surrounding cells make signals that control the branching

2) LOOK for signal proteins and matching receptors that are in the right place for this

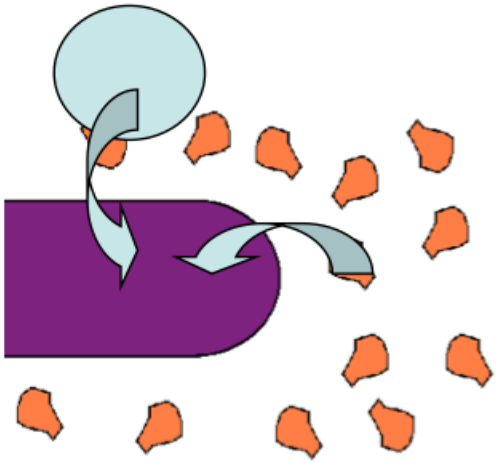
3) TEST to see if they control the bud





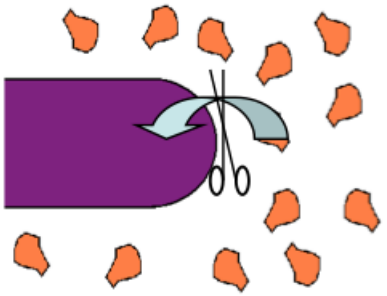


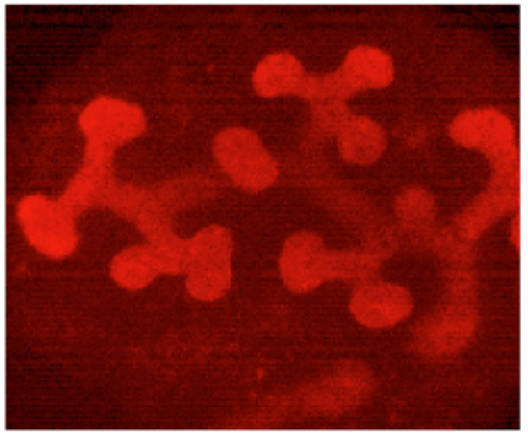
Interrupt the signal



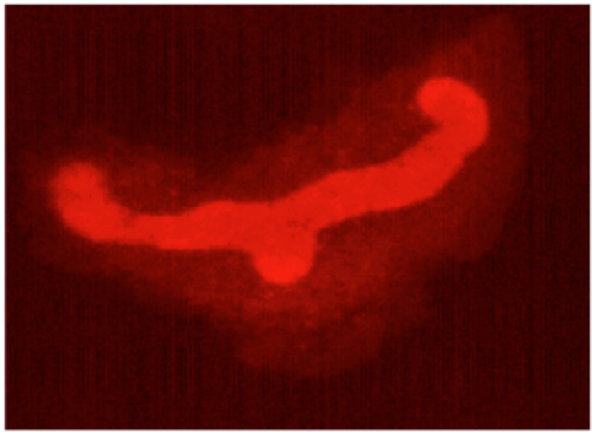
Give a fake signal

Interrupt the signal:



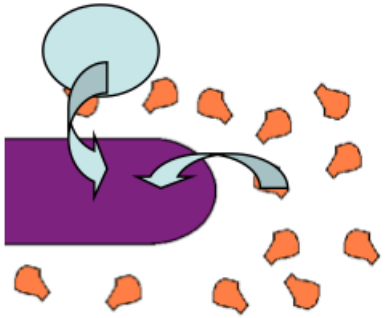


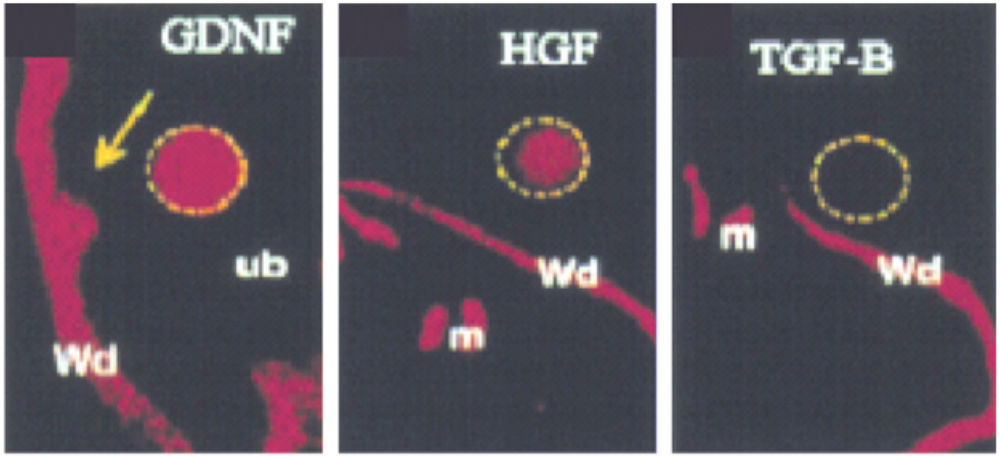
Control (irrelevant) antibody



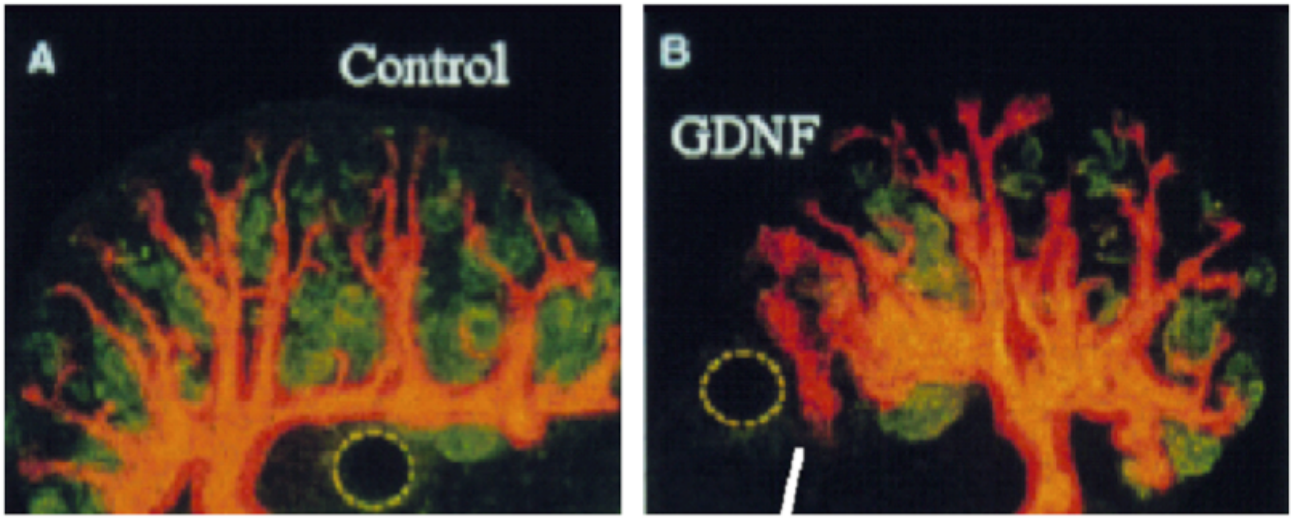
anti-GDNF

Make our own message and see if the cells respond:





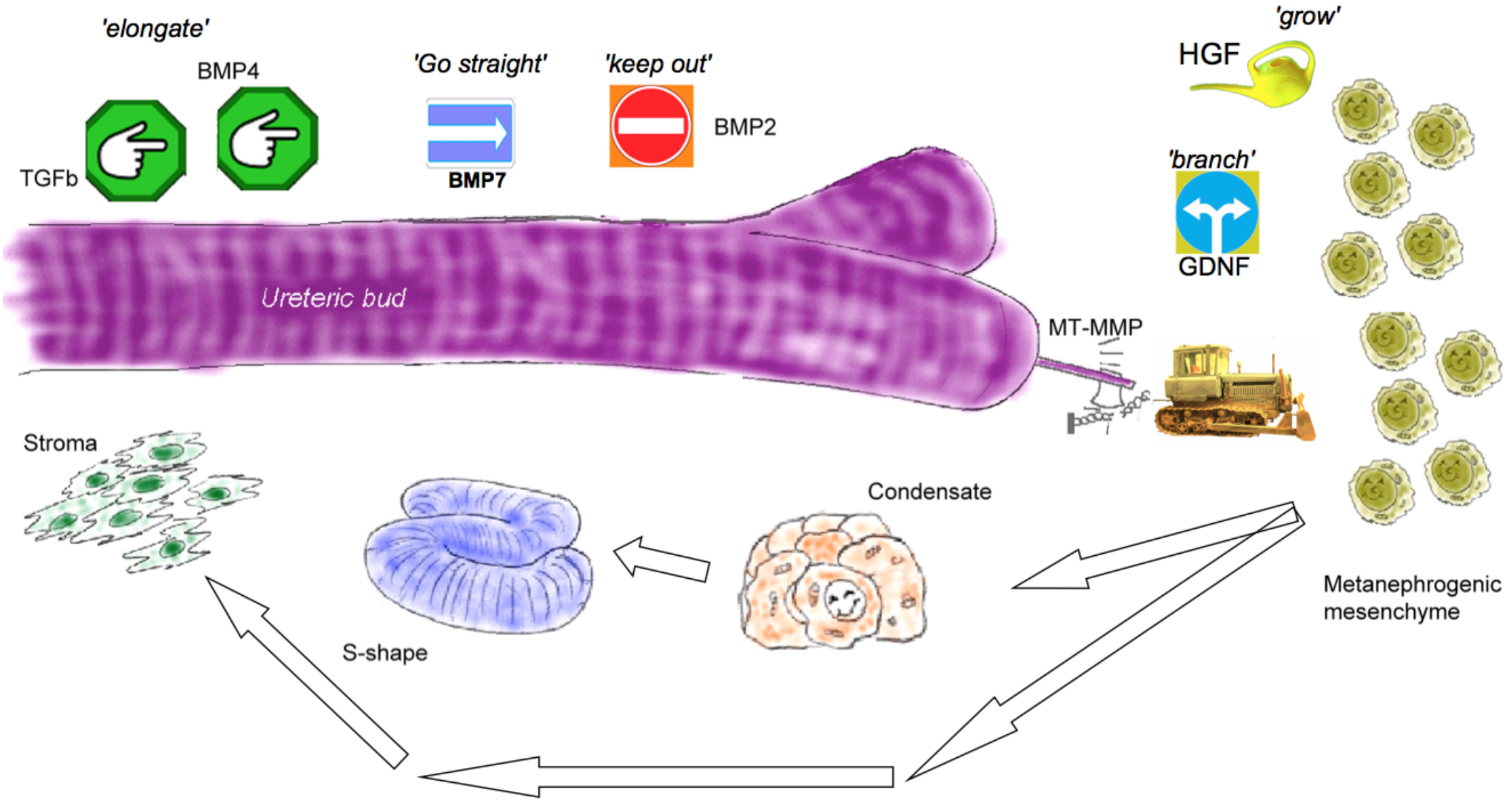
Inducing branches from
the very early tube



Attracting branches from established tubes.

More signals have been discovered using the same approach:

(Signals colour-coded according to source tissue)



Problem 3: how do the branches of the tree avoid getting tangled?

A model of self-loathing:

Model:

UB secretes a substance called 'horrid' – a noise component is also added

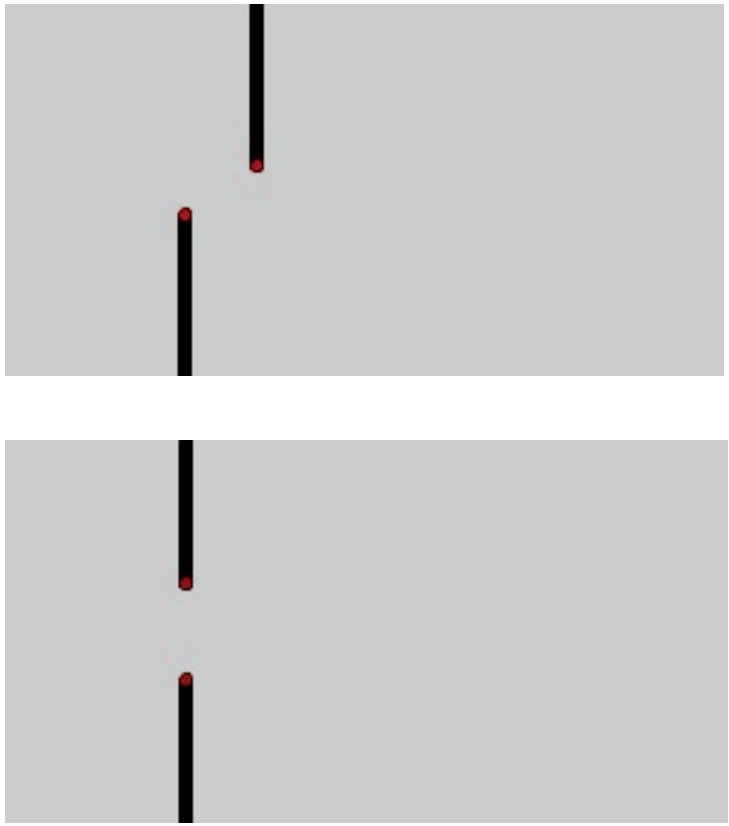
UB tips always grow in the direction of least [horrid]

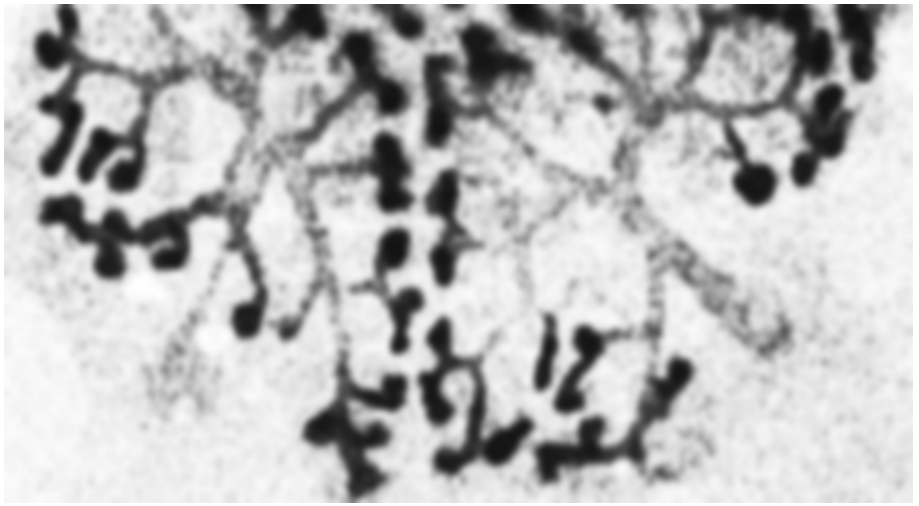
UB branches (1 tip → 2 adjacent ones) if [horrid] < threshold

(everything is sensed only locally, in the pixels immediately adjacent to each cell's own pixel)

Anatomy [Horrid]

To chase the molecular basis, we need an easier assay: attempted collision.





Real

Experimental method:

Culture kidneys aimed at one another

Experimental method:

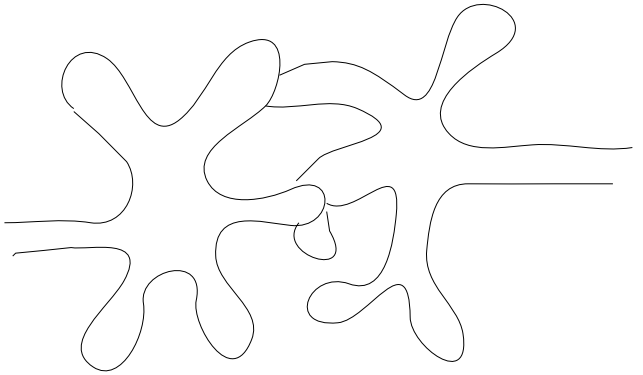
Culture kidneys aimed at one another

Add various test drugs (ideally ones that hit whole classes of signalling molecules)

Experimental method:

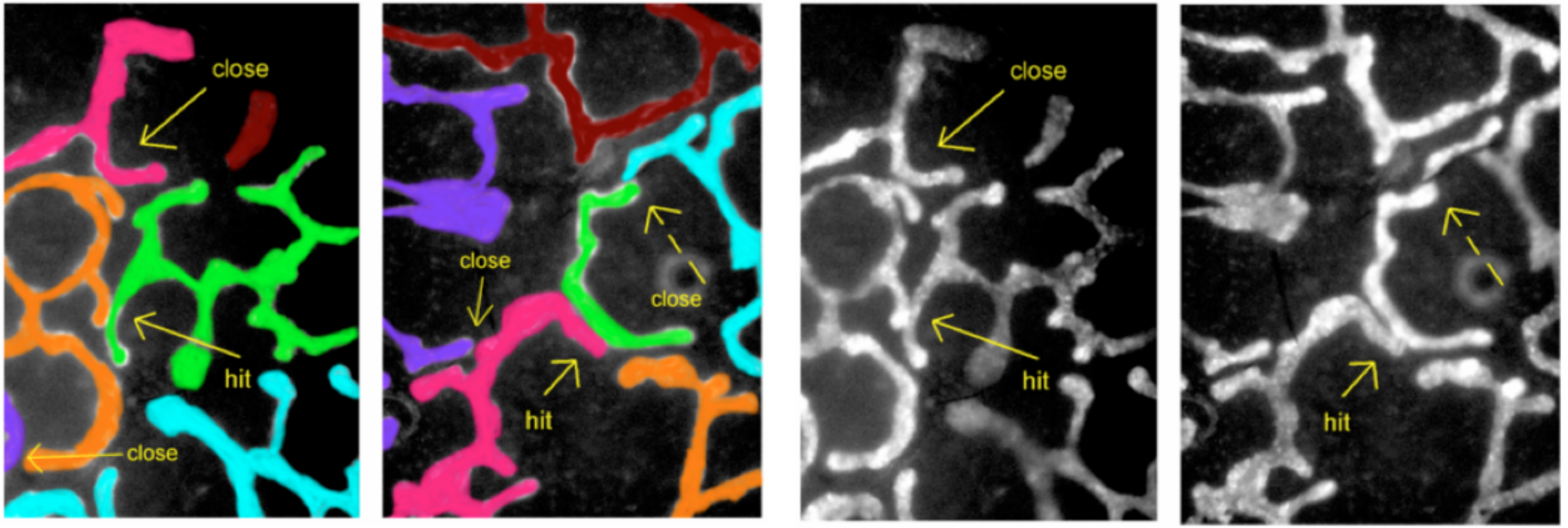
Culture kidneys aimed at one another

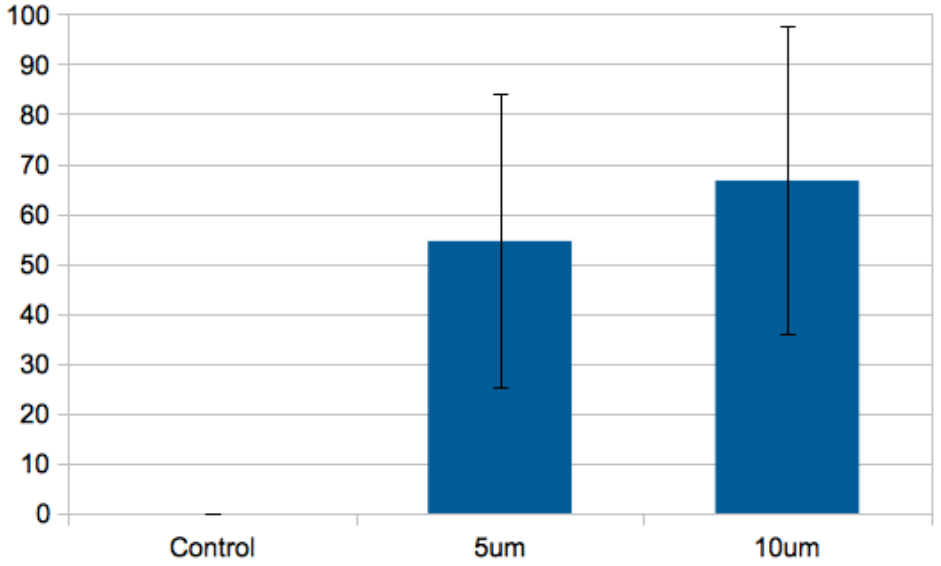
Add various test drugs (ideally ones that hit whole classes of signalling molecules)



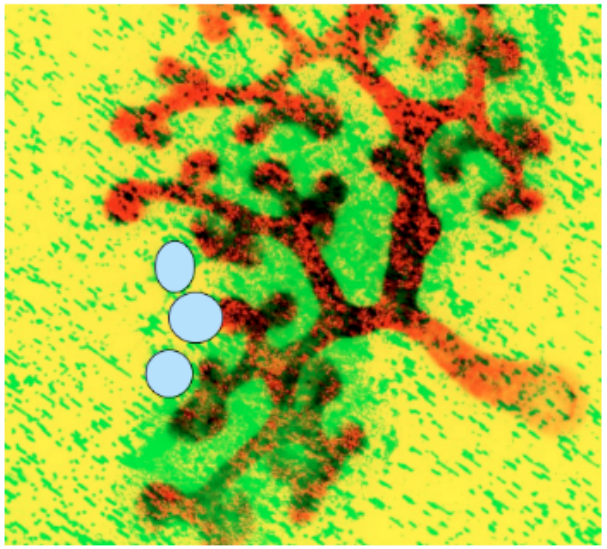
Hope to see a crash.

Alk Inhibitor data

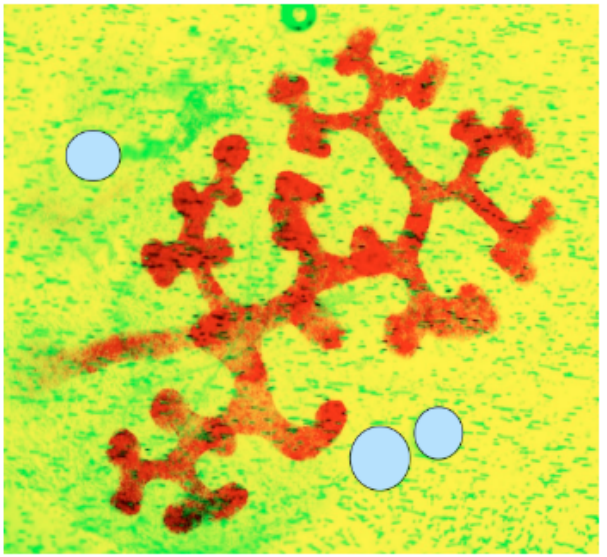




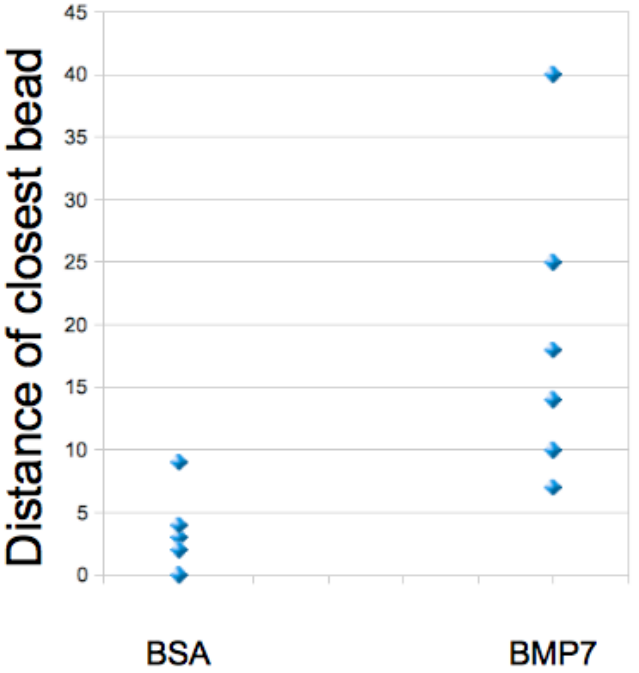
Experimental sources of BMP7



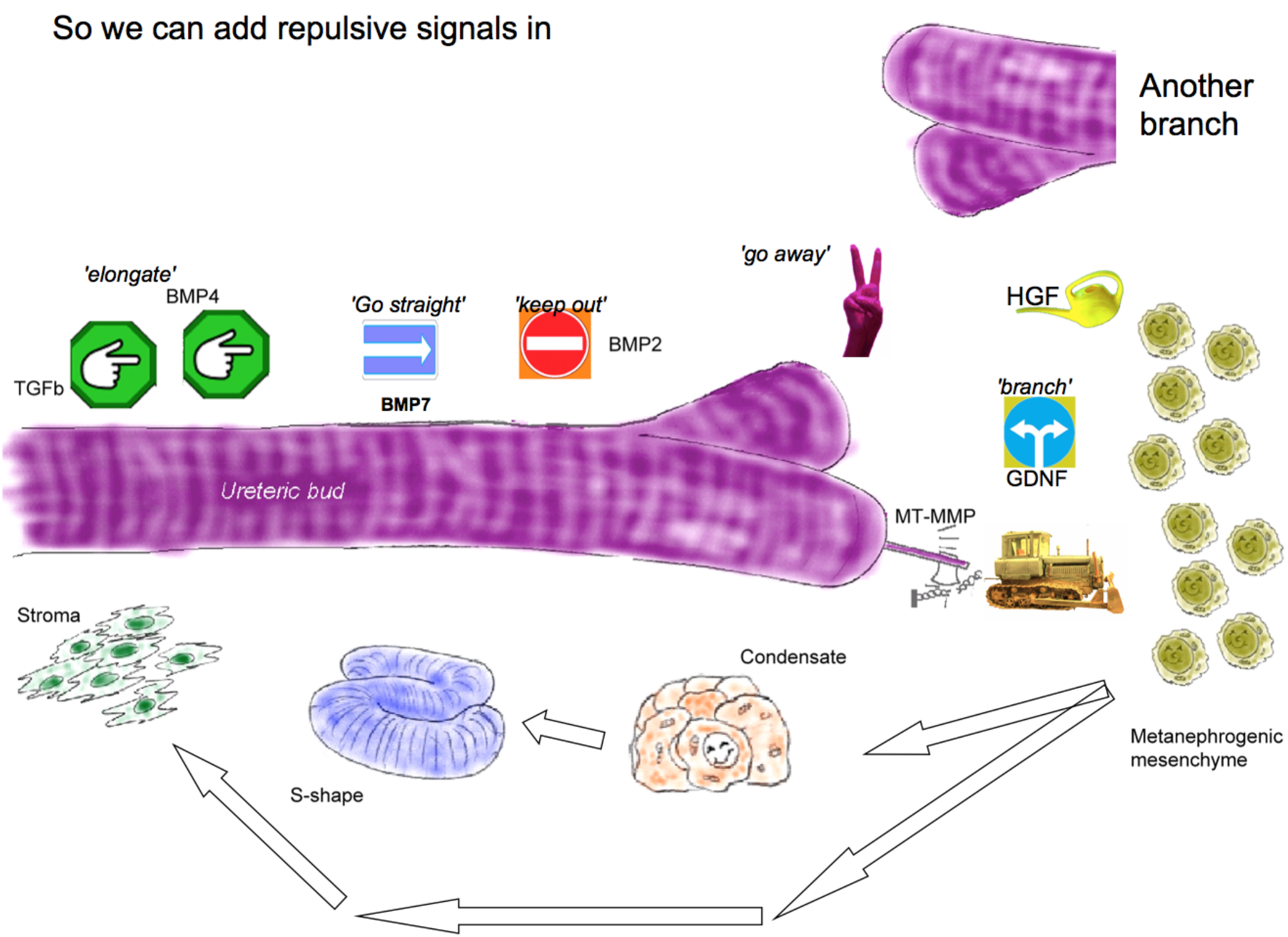
BSA beads



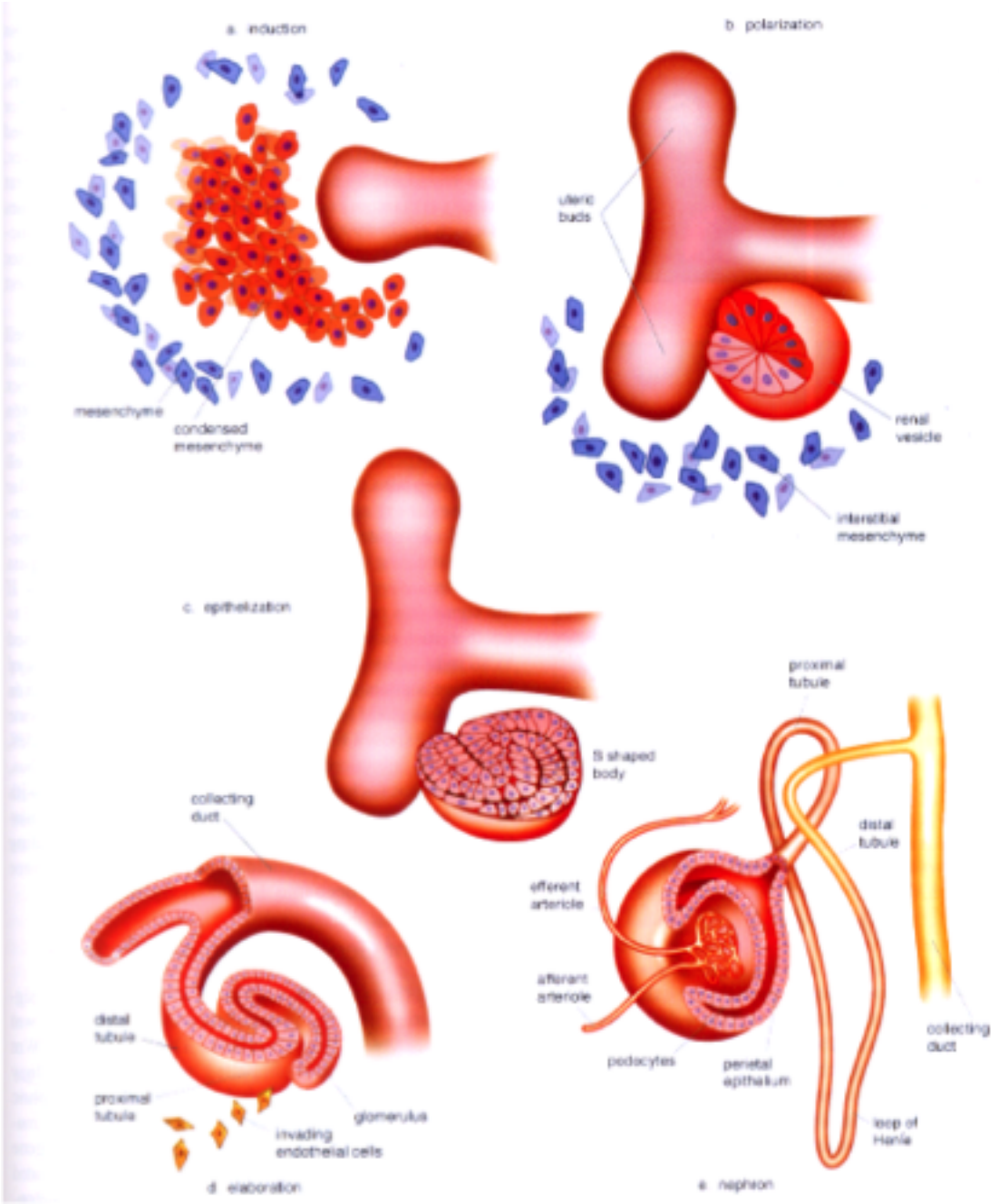
BMP7 beads



So we can add repulsive signals in

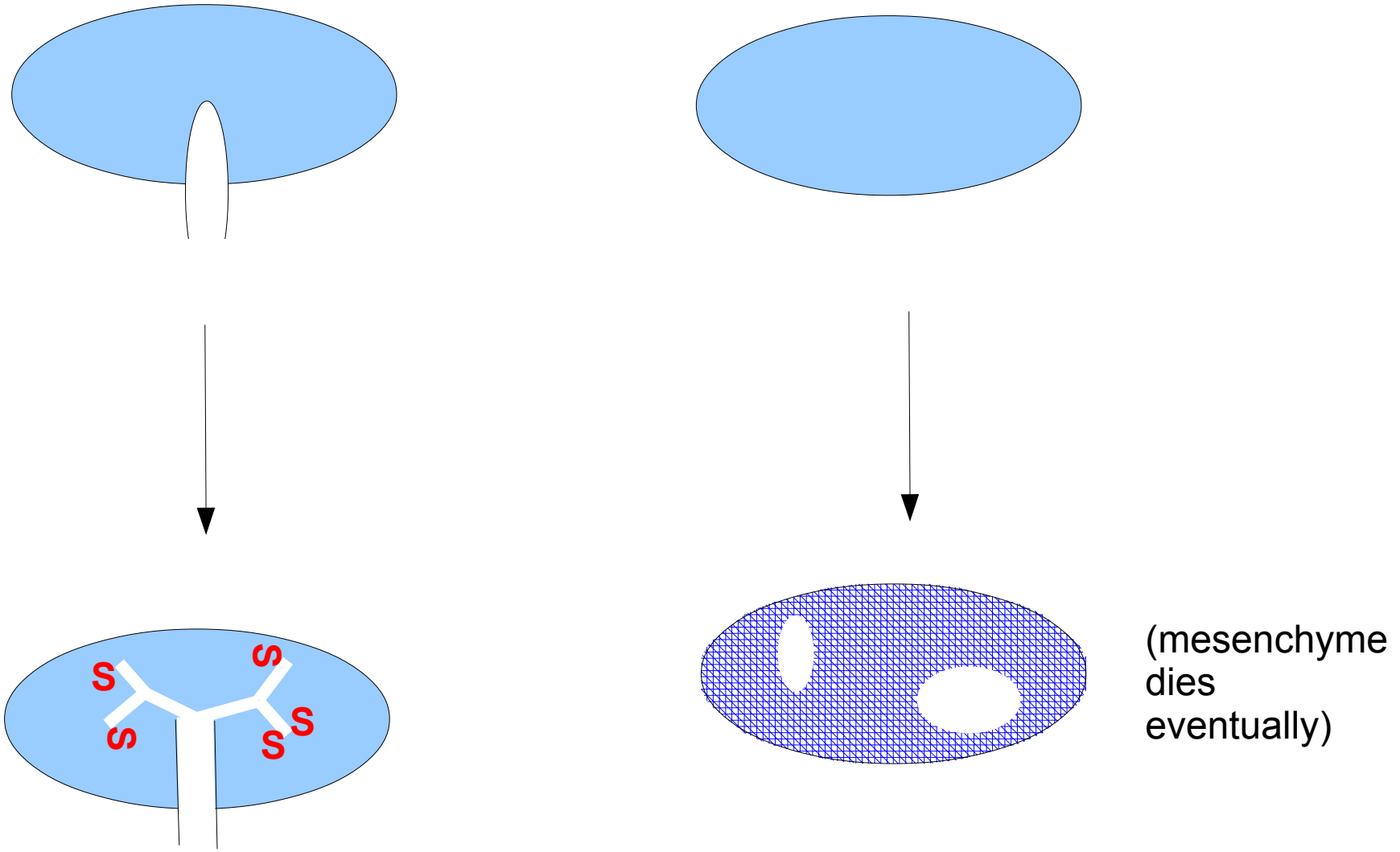


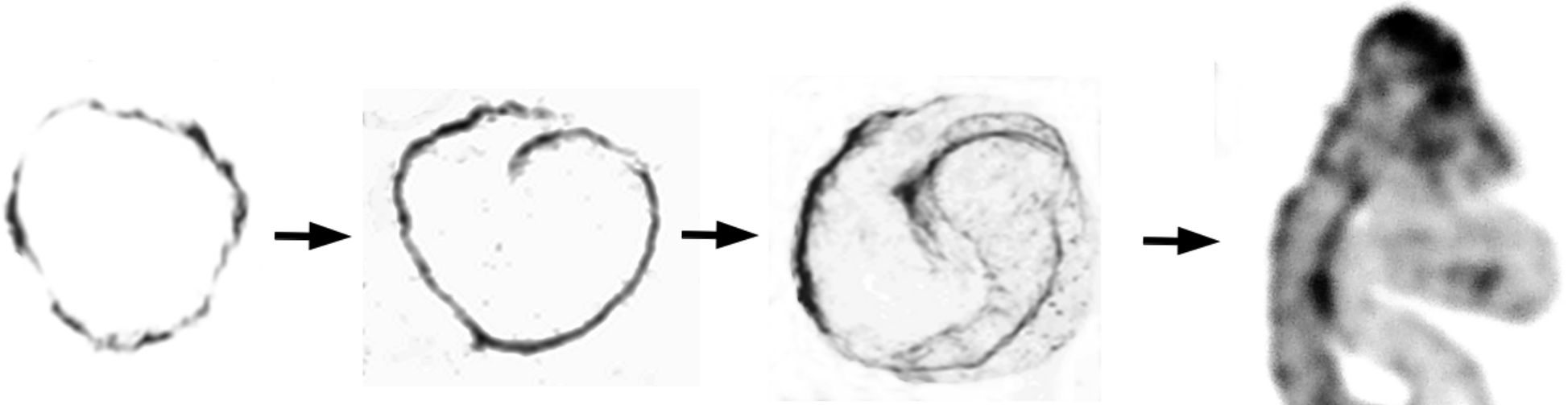
The excretory nephrons have a separate origin from the ureteric bud;


a induction
mesenchyme
condensed mesenchyme
b polarization
ureteric buds
renal vesicle
interstitial mesenchyme
c epithelization
S shaped body
collecting duct
distal tubule
proximal tubule
glomerulus
invading endothelial cells
d elaboration
proximal tubule
distal tubule
efferent arteriole
afferant arteriole
collecting duct
podocytes
parietal epithelium
loop of Henle
e nephron

Problem 5: how to the nephrons form near the bud branches?

The ureteric bud is needed for neprhons to form in the mesenchyme





renal vesicle

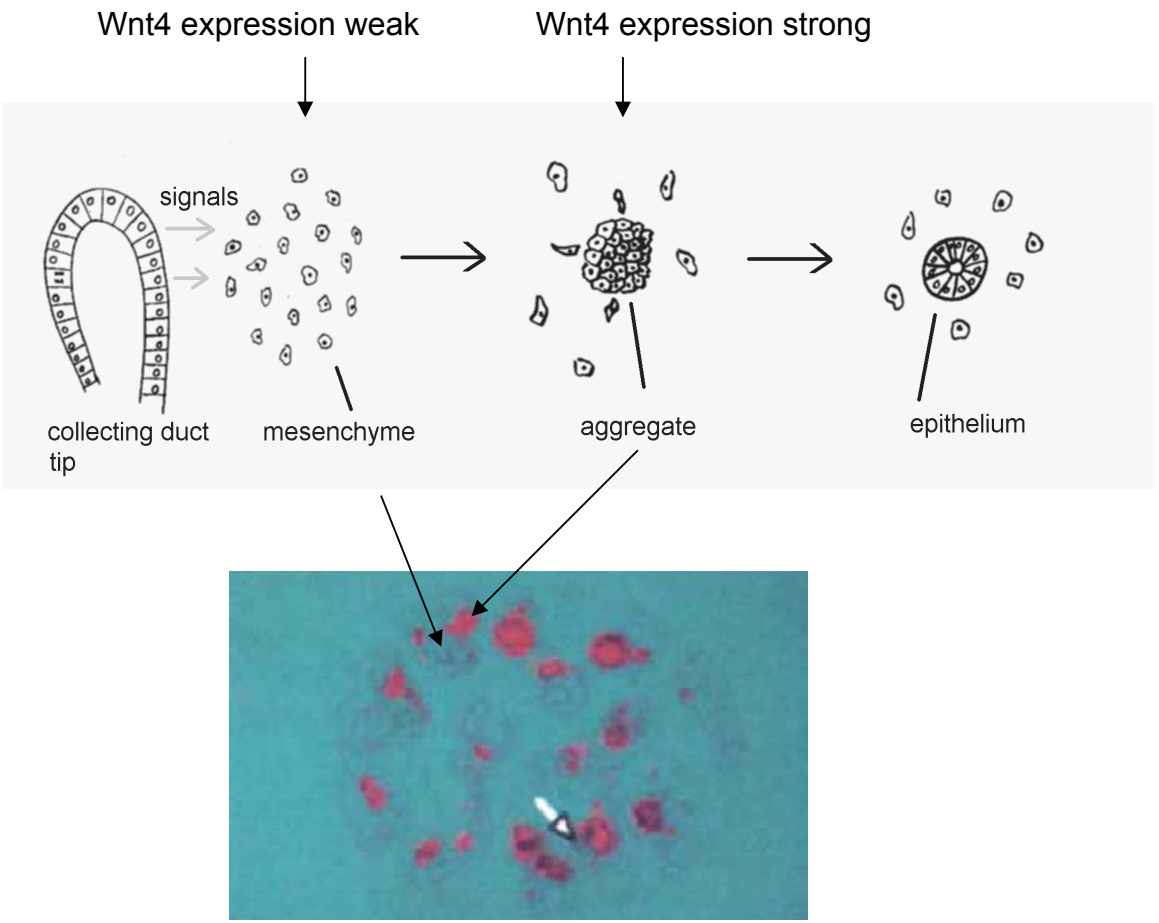
comma-shape

'S'-shape

Maturing nephron
(lower magnification)

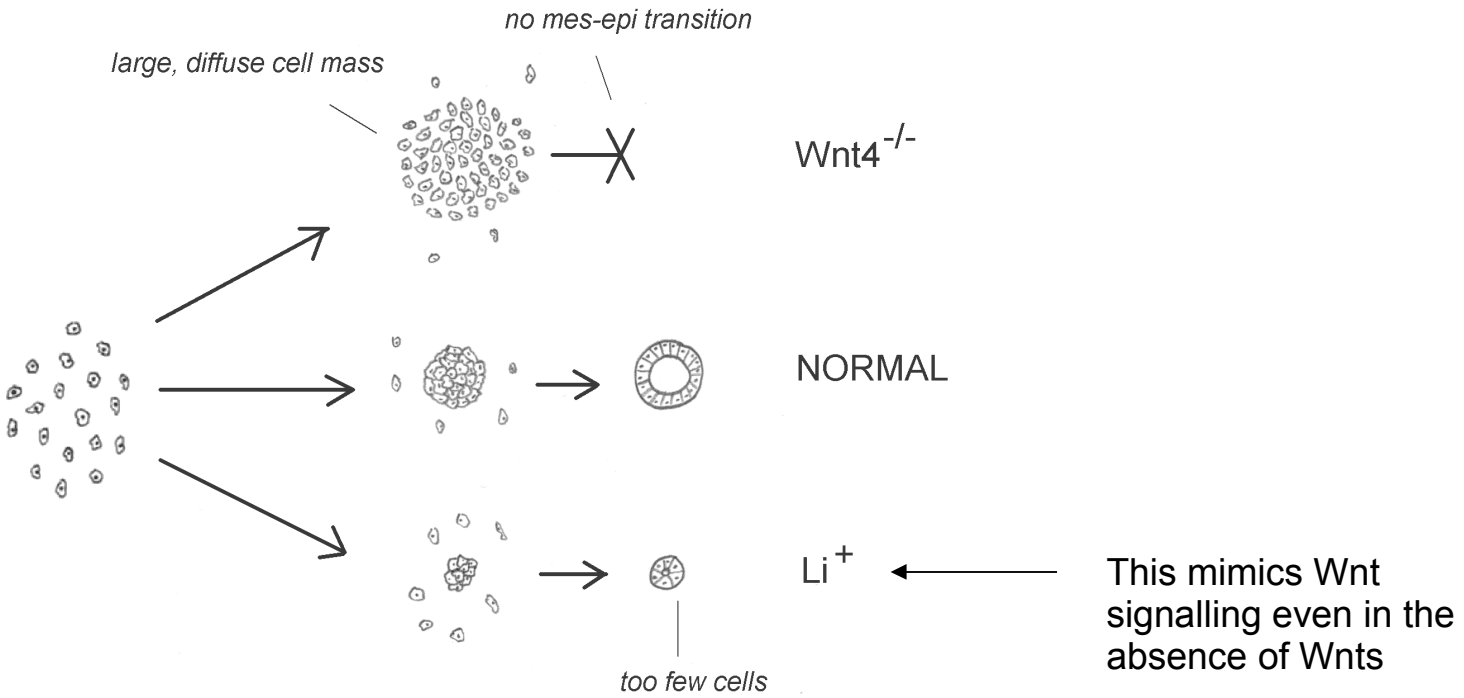
Problem 6 – how do mesenchyme cells make a large enough aggregate to make a nephron?

Evidence for quorum sensing: the kidney



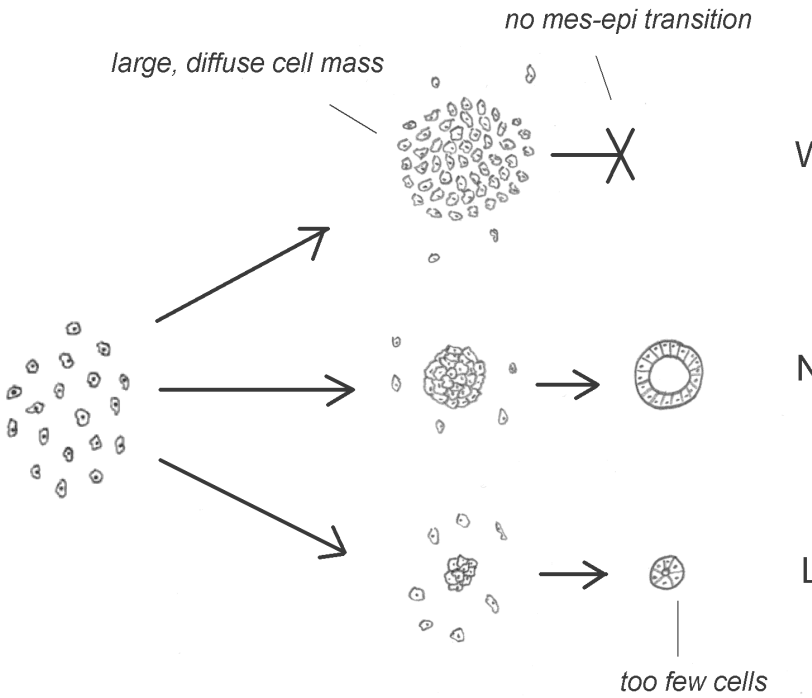
Ref: Davies JA (2005) *Mechanisms of morphogenesis*

Evidence for quorum sensing: the kidney



Ref: Davies JA (2005) *Mechanisms of morphogenesis*

Evidence for quorum sensing: the kidney

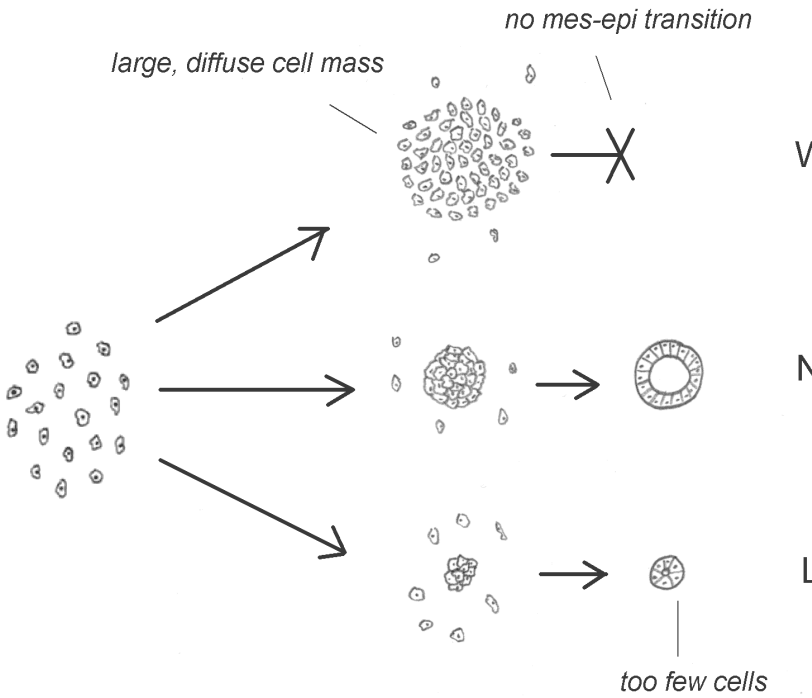


Cells have no way of knowing they have made a big enough aggregate

This mimics Wnt signalling even in the absence of Wnts

Ref: Davies JA (2005) *Mechanisms of morphogenesis*

Evidence for quorum sensing: the kidney

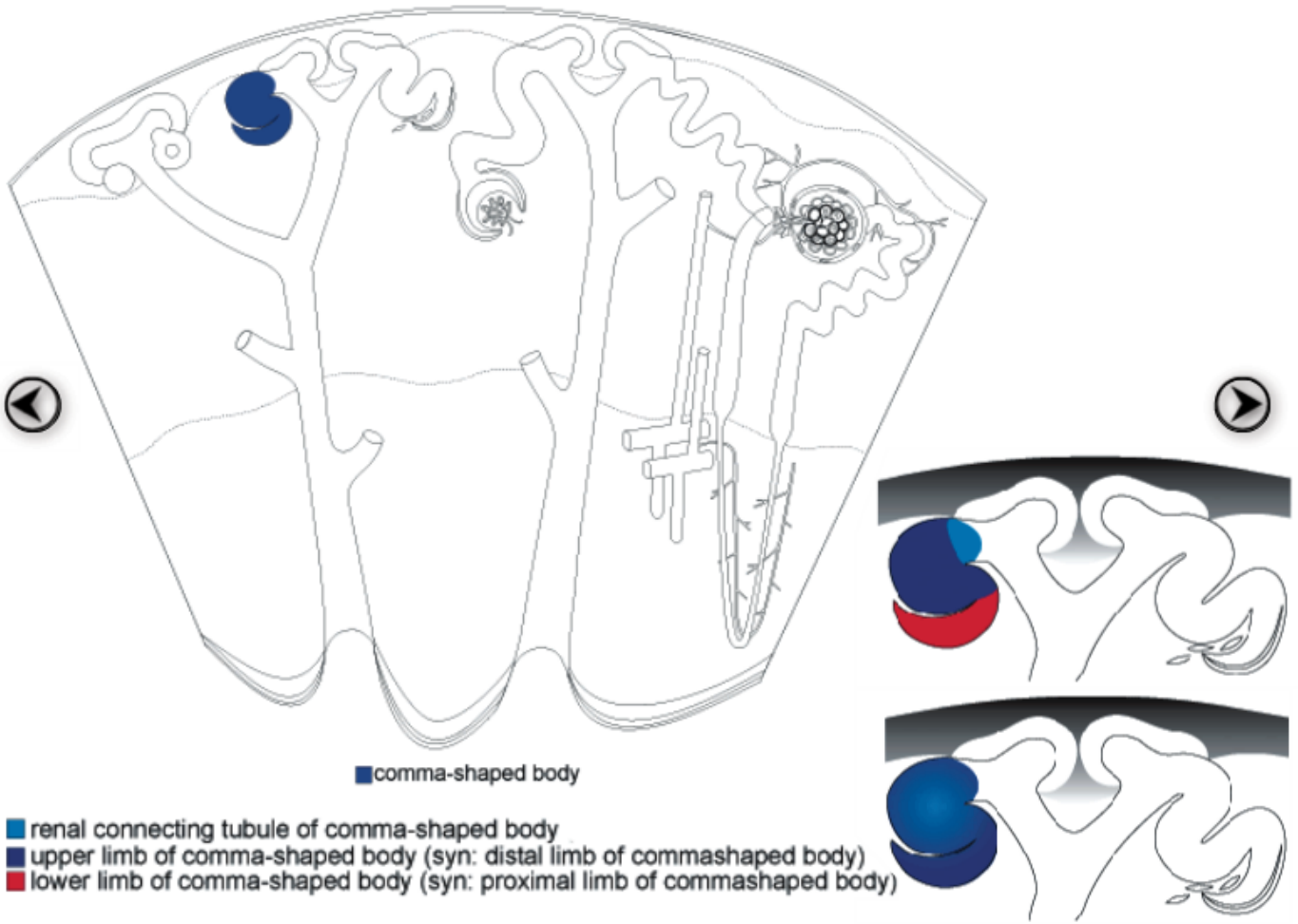


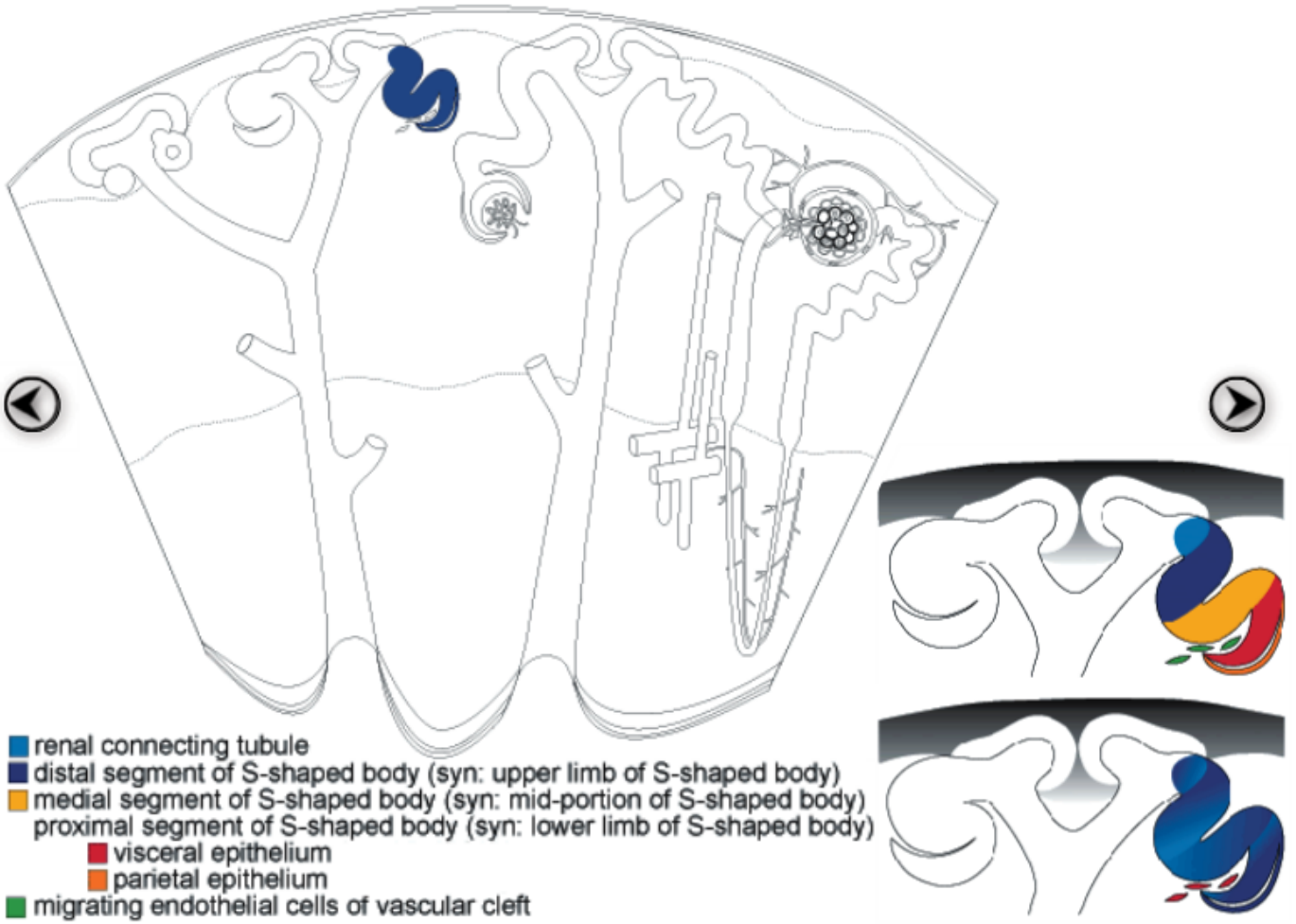
Cells have no way of knowing they have made a big enough aggregate

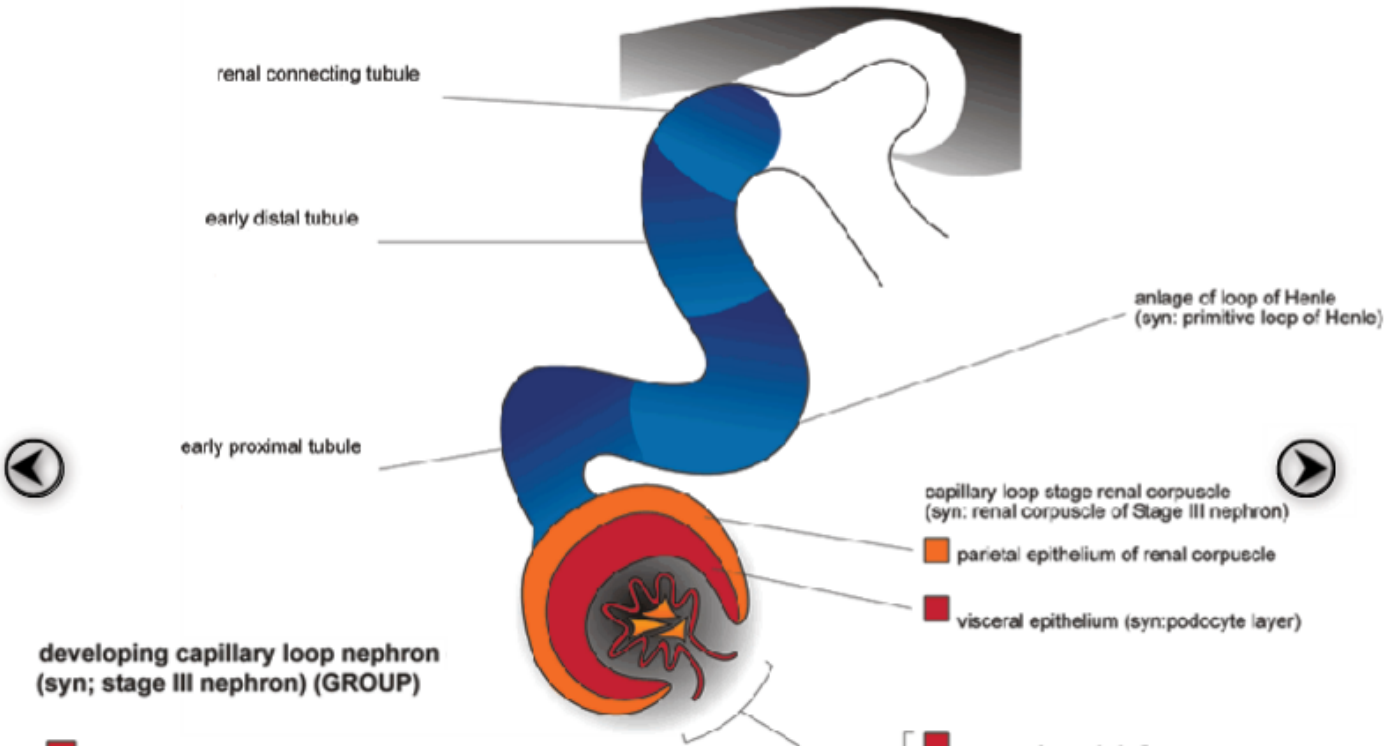
This mimics Wnt signalling even in the absence of Wnts

Cells think the aggregate is already big

Ref: Davies JA (2005) *Mechanisms of morphogenesis*


comma-shaped body
renal connecting tubule of comma-shaped body
upper limb of comma-shaped body (syn: distal limb of commashaped body)
lower limb of comma-shaped body (syn: proximal limb of commashaped body)


renal connecting tubule
distal segment of S-shaped body (syn: upper limb of S-shaped body)
medial segment of S-shaped body (syn: mid-portion of S-shaped body)
proximal segment of S-shaped body (syn: lower limb of S-shaped body)
visceral epithelium
parietal epithelium
migrating endothelial cells of vascular cleft

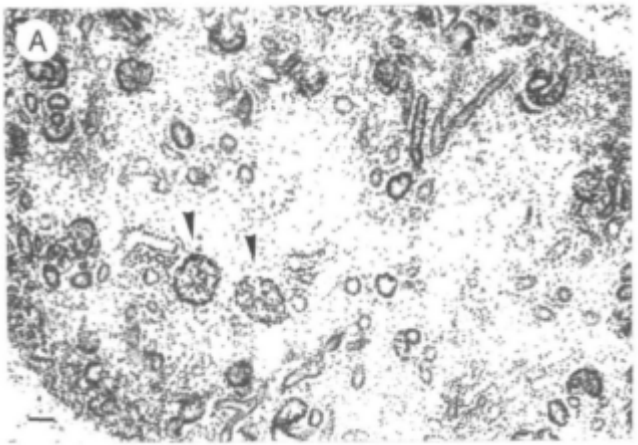

renal connecting tubule
early distal tubule
anlage of loop of Henle
(syn: primitive loop of Henle)
early proximal tubule
capillary loop stage renal corpuscle
(syn: renal corpuscle of Stage III nephron)
parietal epithelium of renal corpuscle
visceral epithelium (syn:podocyte layer)
developing capillary loop nephron
(syn; stage III nephron) (GROUP)
capillary loop stage renal corpuscle (syn: renal corpuscle of Stage III nephron)
associated interstitium of renal corpuscle
parietal epithelium of renal corpuscle
presumptive endothelium
presumptive mesangium
visceral epithelium (syn:podocyte layer)
cortical renal tubule (syn:tubular portion of nephron)
early distal tubule
anlage of loop of Henle (syn: primitive loop of Henle)
early proximal tubule
renal connecting tubule
presumptive endothelium
presumptive mesangium
associated interstitium of renal corpuscle

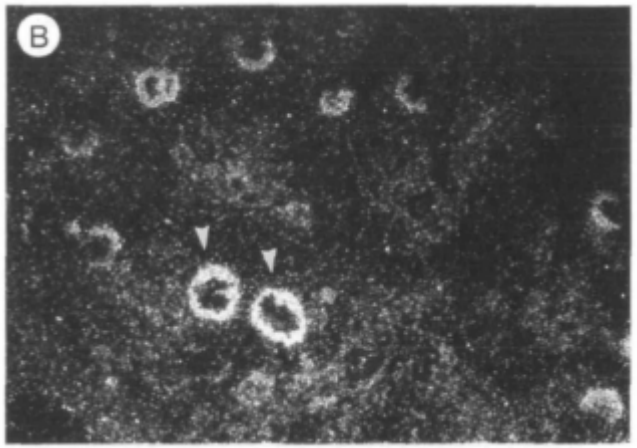
Problem 7: how do blood vessels find glomeruli?

Development 114, 521-532 (1992)
Printed in Great Britain © The Company of Biologists Limited 1992

Expression of vascular endothelial growth factor during embryonic angiogenesis and endothelial cell differentiation

GEORG BREIER, URSULA ALBRECHT, SYLVIA STERRER* and WERNER RISAU





Brightfield

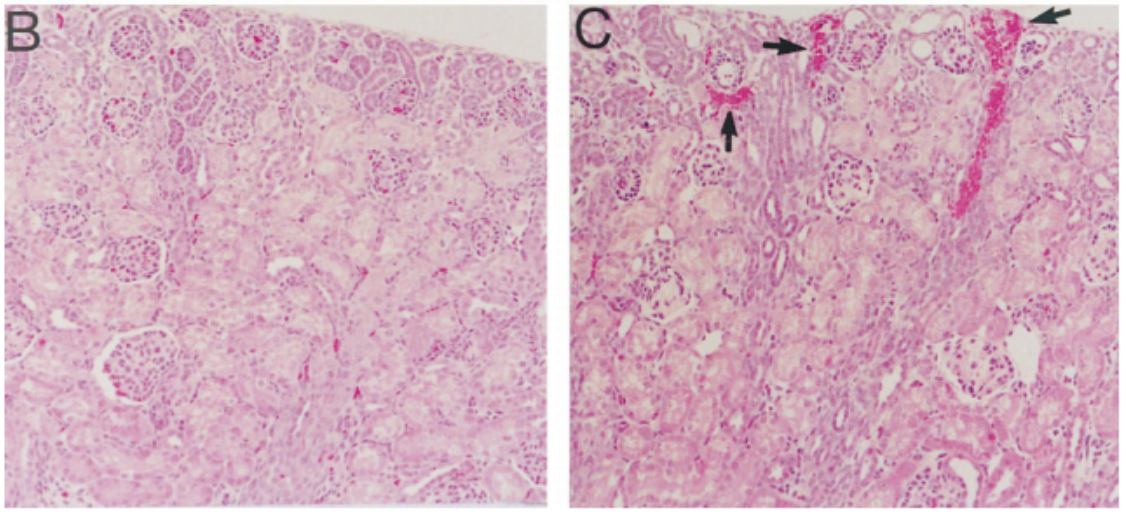
ISH (NB glomeruli)

Loss of the $VEGF_{164}$ and $VEGF_{188}$ Isoforms Impairs Postnatal Glomerular Angiogenesis and Renal Arteriogenesis in Mice

VIRGINIE MATTOT,* LIEVE MOONS,* FLOREA LUPU,§ DANIEL CHERNAVVSKY,†
R. ARIEL GÓMEZ,† DÉSIRÉ COLLEN,* and PETER CARMELIET*

Vascular Endothelial Growth Factor Is an Essential Molecule for Mouse Kidney Development: Glomerulogenesis and Nephrogenesis

Yasunori Kitamoto, Hiroshi Tokunaga, and Kimio Tomita
Third Department of Internal Medicine, Kumamoto University School of Medicine, Kumamoto 860, Japan



Normal

Congested large vessels,

'empty' glomeruli

Model: developing glomeruli produce VEGF that attracts blood vessels.

SUMMARY of the kidney story (not quite the end of the lecture)

Ureteric bud emergence from WD depends on balance of permissive (GDNF) and inhibitory (BMP4) signals from other tissues.

Branching of ureteric bud is encouraged by positive signals (GDNF) from 'virgin' metanephrogenic mesenchyme and discouraged by negative signals (BMP2, TGFb) from nephron-forming areas.

Branches space out by self-loathing (secreting BMP7)

Nephrons form in response to Wnt9b from branch tips

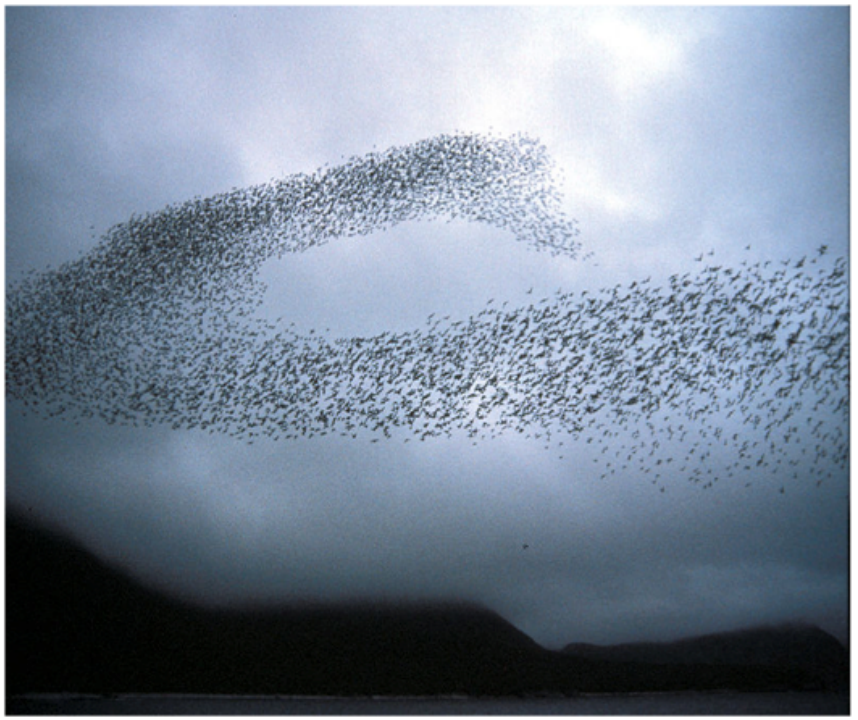
Pre-nephron aggregates sense their size by autocrine Wnt4

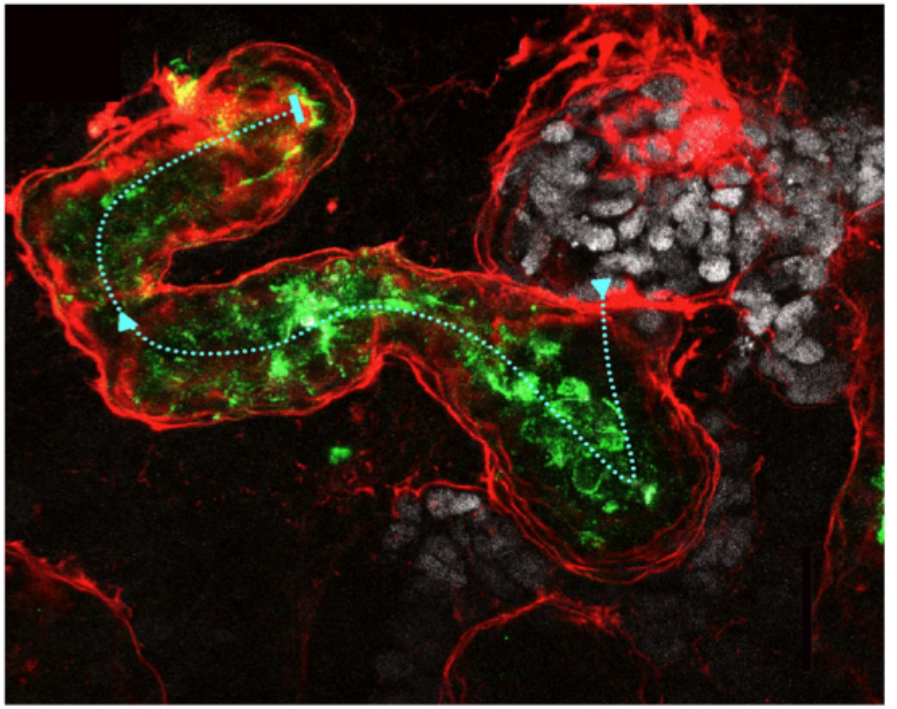
Developing glomeruli secrete VEGF to attract blood vessels.

In this way, the whole system is adaptive and self-corrective, and cells can make something much larger than themselves.

THERE IS STILL VERY MUCH THAT WE DO NOT UNDERSTAND

The Bottom line: the organ organizes itself cells exchanging simple messages with their neighbours, in a biochemical code.

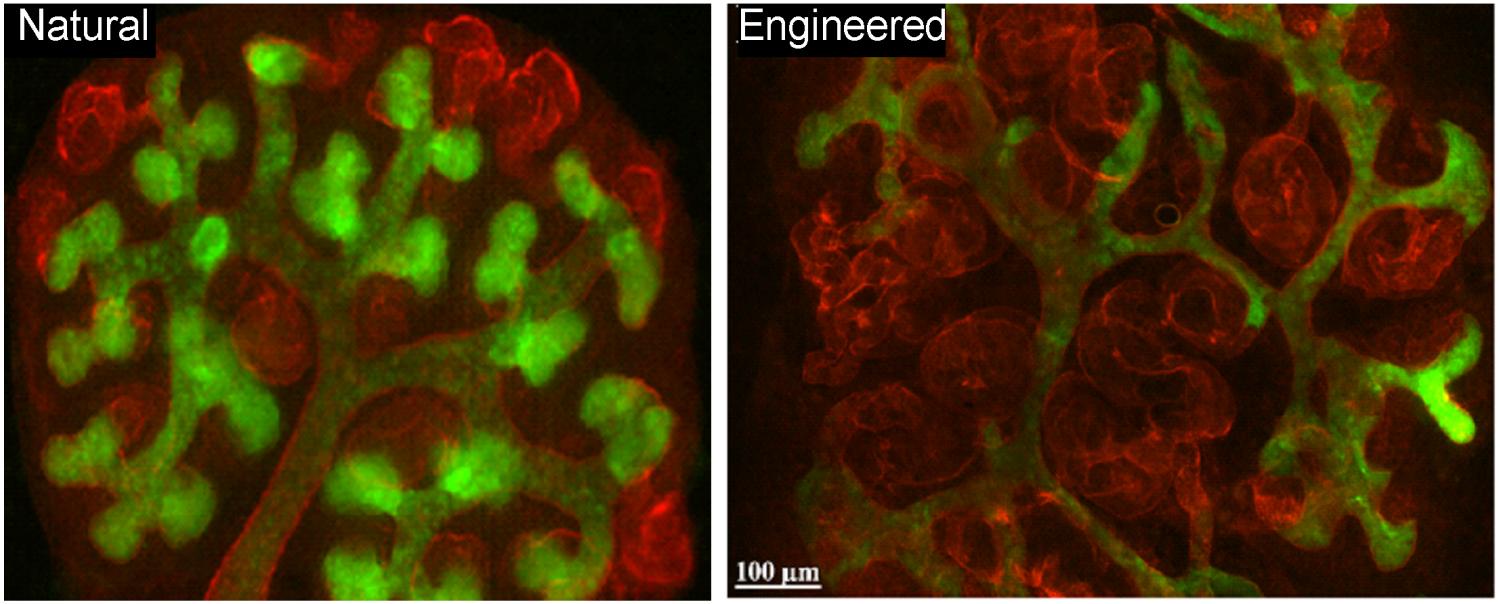




(ignore the arrow)

Images: Birds - D Dibenski: Creative commons; nephron: Nils Lindström

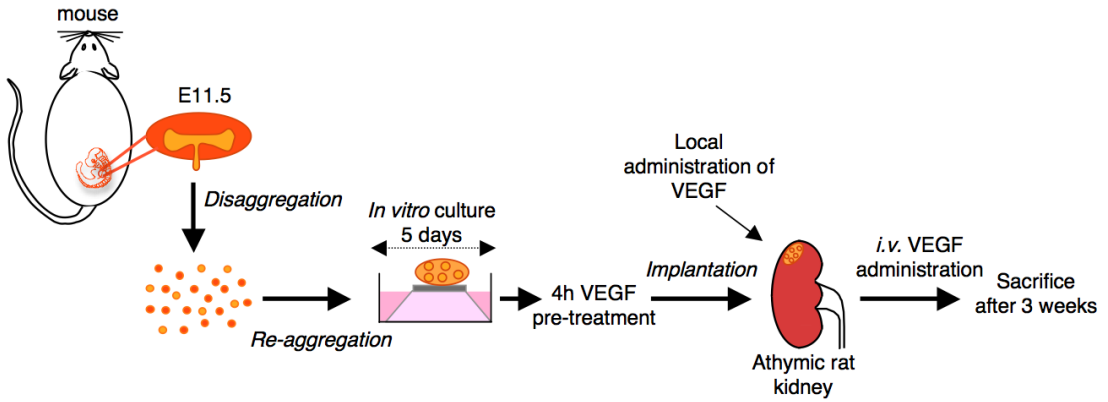
(Off-syllabus tangent; we can *use* our knowledge of cell-cell communication to engineer replacement organs)



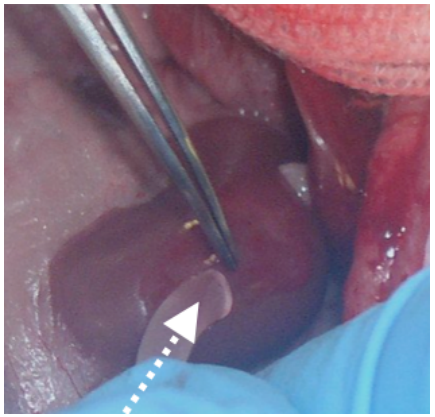
Mathieu Unbekandt, Veronica Ganeva.

Ganeva et al. 2011

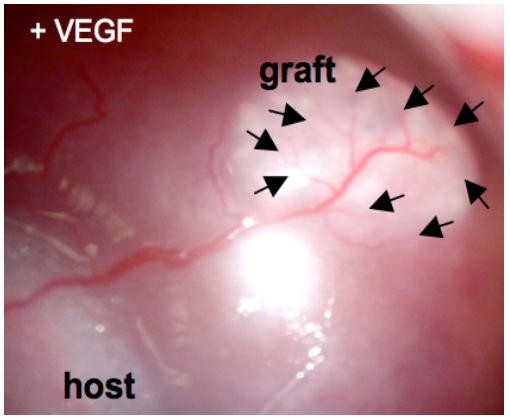
With our colleagues in Italy, we have tested these kidneys in rats:



Grafting

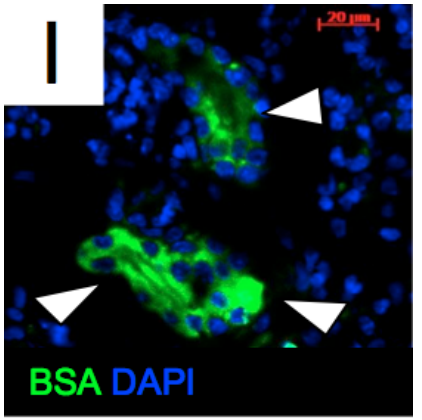


After some weeks



i.v. injection of fluorescent SA

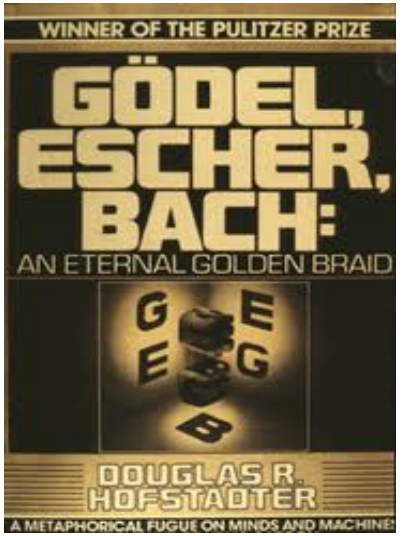
SA turns up in prox tubule



C. Xinaris, V. Benedetti, P. Rizzo, M. Abbat, D. Corn, N. Azzolini, M. Unbekandt, JA Davies, M. Morigi, A. Benigni, and G. Remuzzi
Manuscript submitted

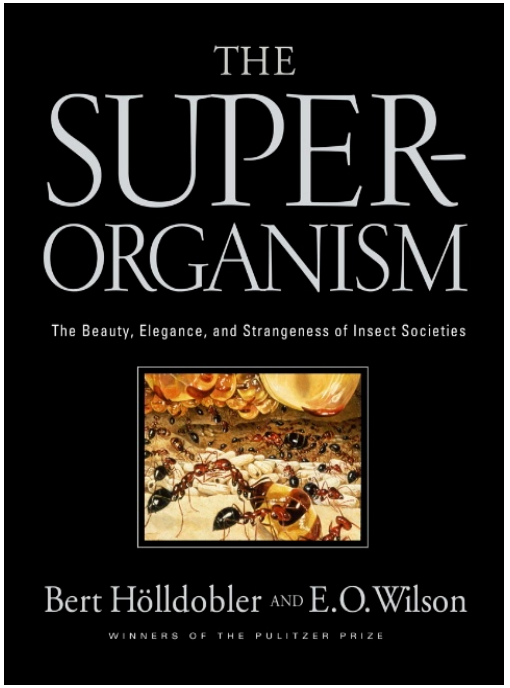
CLOSING REMARKS – CAN WE DRAW 'BIGGER' CONCLUSIONS?

Aunt Hillary



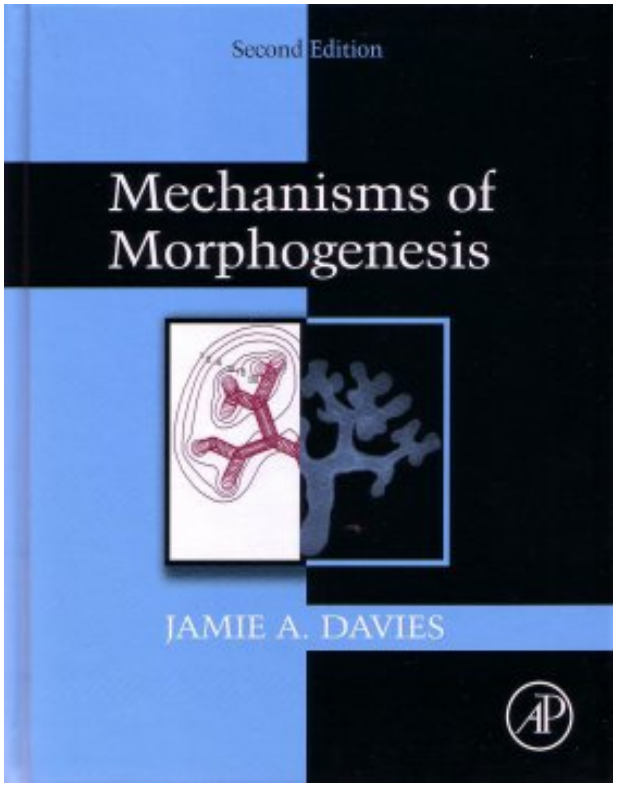
(One of the most fun science books ever written)

Excellent (serious) book on this stuff

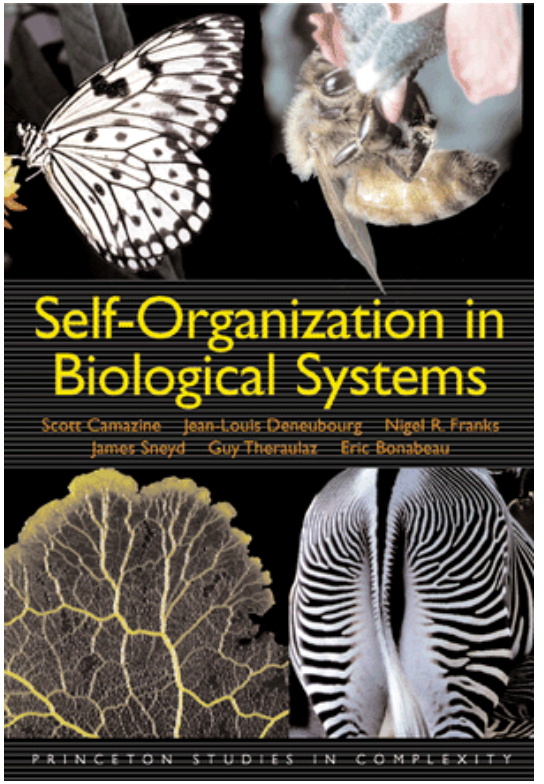


SQUIRES
KEN JACKSON

Further reading (if you feel like it – this is not on any exam syllabus)



(My own book, specifically about self-organization in development)



(An excellent multi-author book about self-organization in general)